

NOVEL REACTIONS
OF HALOMETHYLTRIALKYLAMMONIUM SALTS

By

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To my Heavenly Father:
"I will praise thee forever, because
Thou hast done it...." *Ps. 52:9*

To Mom, Dad, Celia, Angela, and my church family:
Thanks for believing in me.

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Recently, it has become quite trendy for entertainers, sports icons, and other famous people to thank God whenever they accomplish a major feat. As I express my thanks to my heavenly Father, I do not wish to merely follow a trend. I am sincerely grateful to my Lord Jesus Christ who has not only granted me the opportunity to learn, but also to excel in chemistry to the point of obtaining the degree of Doctor of Philosophy.

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Abstract of Dissertation Presented to the Graduate School
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By

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Major Department: Chemistry

Depending on the reaction conditions, radical or nucleophilic substitution reactions may be induced from the same halomethyltrialkylammonium salts.

α -Ammonio distonic radical cations are generated by means of either thermal or photochemical initiation of these salts in solution. Once generated, these radical cations show reactivity similar to that of inert alkyl radicals. Distonic radical cations readily perform hydrogen abstraction and intramolecular alkene additions. In fact, 5-exo-hexenyl cyclizations are so rapid that bimolecular hydrogen abstractions will not compete. Competition between 6-exo-heptenyl cyclization and bimolecular hydrogen abstraction is observed with the cyclization being enhanced by the presence of phenyl substituents on the olefin.

The allyl-substituted ammoniomethylene distonic radical cation performs 4-exo-pentenyl cyclization. This cyclization competes with bimolecular

hydrogen abstraction and unimolecular fragmentation to give the allyl radical, which in turn becomes propene, and the Eschenmoser's salt by-products, trimethylamine and trimethylammonium salt.

Under thermal conditions, halomethyltrialkyl-ammonium salts are de-alkylated by iodide to give the corresponding alkyl iodide and methylene iminium salt. Simple trialkyl-substituted salts are de-alkylated by a bimolecular process that follows a concerted, Grob-like fragmentation mechanism. In cases where there are methyl and ethyl substituents on the same ammonium salt, de-methylation competes with de-ethylation, and is always faster. For the allyldimethylammonium system, only de-allylation occurs. The fragmentation of the substrate occurs by a unimolecular process.

CHAPTER 1 AN OVERVIEW OF RADICAL AND NUCLEOPHILIC SUBSTITUTION REACTIONS

1.1 General Introduction

The organic chemistry of nitrogen-containing compounds is quite vast and has incited a great deal of interest. This is not surprising when one considers that nitrogen is one of the principal elements in all living creatures and as a result, nitrogen-containing compounds are ubiquitous in nature. Applications of nitrogen compounds include natural products such as pancreastatin,¹ and polymers of the type used in photographic material.² Other industrial uses include agricultural products, dyes, amines, and nitro-compounds. Because of the importance of nitrogen in the growth of plants and animals, it is not surprising that nitrogen containing compounds are produced in vast quantities commercially. As a result, many have been encouraged to investigate the chemistry of this large class of organic compounds. While others turn their attention to areas such as heterocyclic chemistry and the chemistry of polyfunctional compounds such as amino acids and nitro alcohols, we focus ours on the versatile chemistry of halomethyltrimethylammonium salts.

The goal of this dissertation is to discuss the novel chemistry of halomethyltrialkyl ammonium salts, the results of which are reported in subsequent chapters. It will therefore be appropriate to review certain concepts that are common to physical organic chemistry. This chapter gives a very

concise overview of free radical chemistry and solvolytic displacement reactions as they pertain to the results that are presented within this dissertation.

1.2 Overview Of Organic Free Radical Reactions



Figure 1-1. The Elementary Mechanistic Pathways of Free Radical Reactions.

In 1900, Moses Gomberg³ discovered the first free radical, that is, the triphenylmethyl radical. It was more than thirty years later that pioneering investigations revealed the primary mechanistic pathways that are available to organic free radicals.⁴⁻⁹ From these studies, it was determined that most radical reactions can be expressed in terms of a small number of discrete processes, or variations thereof, as summarized in Figure 1-1.¹⁰

Organic radicals, as recently as fifteen years ago, were viewed as interesting reactive intermediates with limited synthetic potential. Radical reactions were generally considered to be quite messy and unpredictable with few exceptions, for example, allylic brominations with N-bromo-succinimide.¹¹ Since then, synthetic and thermodynamic studies have caused the scientific world to re-evaluate its view and as a result, radical-molecule reactions are

recognized as very predictable, controllable, and thus, useful methods for accomplishing a multitude of synthetic transformations.¹²⁻¹⁸

Radical Chain Processes

The underlying difference between free-radical reactions and other reaction types (for example, nucleophilic substitution reactions) is that most free-radical reactions are chain reactions: that is, the reaction mechanism involves a sequence of steps that are repetitive. Figure 1-2 shows an example of a radical chain process where two pathways compete.

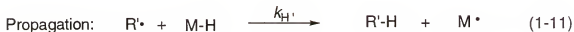


Figure 1-2. Radical Chain Process involving Competition Between Rearrangement vs. Hydrogen Atom Transfer from a Donor Molecule M-H.

In the initiation step, the reactive intermediate, $\text{In}^\bullet$, is generated by homolysis of the initiator, In-In . The homolysis can be accomplished either thermally or photochemically. The presence of $\text{In}^\bullet$ then provides a source of the $\text{M}^\bullet$ radical (Equation 1-7), where $\text{M}^\bullet$ is typically a metal-centered radical, and as a result, $\text{R}^\bullet$ is generated from a suitable precursor, R-X (Equation 1-8). Once $\text{R}^\bullet$ is formed, it will follow one of two pathways: (1) trapping by a hydrogen atom

donor to give R-H (Equation 1-9), or (2) transformation by a unimolecular or bimolecular process (Equation 1-10) to form radical R'· which is eventually trapped to give R'-H (Equation 1-11). In both cases, more M·(Equations 1-8, 1-9, 1-11) is generated which allows the chain process to be propagated.

The reactivity of the radical R· in each elementary step determines the relative distribution of products R-H and R'-H. This is indicated by the rate constants k_H and k_r . If k_H and k_r are comparable, then reactions described in Equations 1-9 and 1-10 are competitive and a mixture of products will be obtained at the end of the reaction. On the other hand, if the rearrangement process is much faster than the hydrogen abstraction, that is, $k_H \gg k_r$, then only R'-H will be detected at the end of the reaction. Understanding the reactivities of any partitioning radical with regard to possible competing processes is therefore essential in designing of useful kinetic experiments and in developing effective synthetic strategy.

Hydrogen Atom Abstraction Reactions

Table 1-1. Bond dissociation energies (M-H), activation parameters and rate constants for hydrogen abstraction by hydrocarbon radicals from R₃M-H.

R ₃ M-H	BDE, kcal/mol	log A	E _a , kcal/mol	^(a) k _H 10 ⁶ M ⁻¹ s ⁻¹
nBu ₃ SnH	73.7	9.06	3.65	2.3
(TMS) ₃ SiH	79.0	8.86	4.47	0.38
nBu ₃ GeH	82.6	8.44	4.70	0.093
(TMS) ₂ Si(CH ₃)H	82.9	8.89	5.98	0.032
Et ₃ SiH	90.1	8.66	7.98	0.00064

^(a)k_H are measured at 298K

Organometallic hydrides of the type R_3M-H (where $M = Sn, Si, Ge$) are commonly used as hydrogen atom donors and chain propagation agents in the majority of free radical applications. The properties of these hydrides have been the focus of extensive investigations by kineticists. Table 1-1 shows the kinetic parameters for the reactions of alkyl radicals with the hydrides R_3M-H .¹⁹⁻²⁶ The related bond dissociation energies (BDE) are also shown.

From Table 1-1, it is evident that the pre-exponential term, $\log A$, remains relatively constant with respect to the radical reducing agent. The variations in the rate constants then are almost entirely due to the differences in the activation energies (E_a), which can be correlated with their relative M-H bond dissociation energies.

Frontier Molecular Orbital (FMO) Theory of Atom Abstraction Reactions

The kinetic characteristics of hydrogen abstraction reactions of free radicals may be explained by using the Frontier Molecular Orbital (FMO) Theory. The frontier orbital of a radical, (a species that contains an unpaired electron) is the singly occupied molecular orbital (SOMO). When the radical is in the ground state, the SOMO is its highest occupied orbital. The FMO theory states that during the course of a radical reaction, the SOMO will interact with both the highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbitals of the reacting molecule.²⁷ The energy values of these frontier orbitals govern the extent of the SOMO-HOMO and SOMO-LUMO interactions.

Radicals may be described as nucleophilic or electrophilic, depending on the effects of neighboring groups on the radical center. In general, electron donating substituents cause both the HOMO and LUMO energies of the radical to be increased, which in turn causes the radical to behave in a nucleophilic

manner. On the other hand, electron withdrawing groups lower the energies of the HOMO and LUMO, giving rise to an electrophilic species (Figure 1-3).

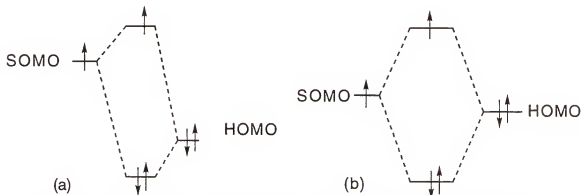


Figure 1-3. Depiction of FMO interactions between the SOMO of different radicals and the HOMO of a donor; (a) a nucleophilic alkyl radical, (b) an electrophilic alkoxy radical.

Figure 1-3(a) shows the interaction between the SOMO of an ordinary alkyl radical with a the HOMO of a donor. The alkoxy radical experiences a more stabilized interaction with the same donor as shown in Figure 1-3(b). As a result, the activation barrier is lowered and a more facile transfer reaction occurs.²⁷

Addition of Radicals to Alkenes

The addition of radicals to olefins has become a very important process among the many methods for forming carbon-carbon bonds. The fact that the radicals may be generated from a variety of precursors under mild conditions allows this method to be advantageous over ionic processes.

Radical additions to unsaturated bonds are highly exothermic due to the formation of a new σ -bond with the concurrent loss of a π -bond. An example of such a transformation is shown in Figure 1-4 where a methyl radical is added to ethylene. The heat of reaction is about -22.6 kcal/mol.²⁸⁻²⁹ According to

Hammond's Postulate,³⁰ which states "if two states, as for example, a transition state and an unstable intermediate, occur consecutively during a reaction process and have nearly the same energy content, their interconversion will involve only a small reorganization of molecular structure," the transition states of these reactions are early, that is, reactant-like, with low activation barriers. This postulate is supported by numerous experimental³¹ and theoretical data.^{28, 32-36}

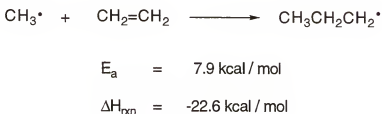


Figure 1-4. Addition of the methyl radical to ethylene producing an *n*-propyl radical.

Intramolecular radical additions to unsaturated bonds, otherwise called radical cyclizations, have become very important within the last decade. Synthetically, these reactions are vital in the preparations of many cyclic organic molecules. Radical cyclizations have attracted a great deal of interest as many continue to study their kinetic, regioelectronic and stereoelectronic characteristics.

A very popular class of intramolecular cyclizations, both for mechanistic study and for synthetic application, is the hexenyl radical cyclization (Figure 1-5).³⁷ These cyclizations are typically irreversible at normal operating temperatures (-80°C to +120°C). For the most part, 5-exo cyclizations are favored over their 6-endo counterparts, primarily for stereoelectronic reasons.

Because of the numerous studies that have been performed, it is now possible to predict the regioselectivities of new substrates with good level of confidence.

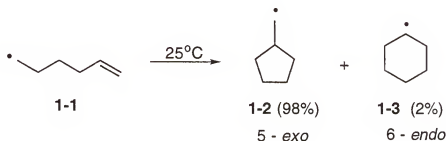


Figure 1-5. Intramolecular cyclization of hex-5-en-1-yl radical to give cyclopentylcarbinyl (1-2) and cyclohexyl (1-3) radicals. At 25°C, 5-*exo* closure is favored 49:1.

Just as hexenyl radicals are known to close in an *exo* or *endo* fashion, heptenyl and related radicals can cyclize in a 6-*exo* and 7-*endo* manner (Figure 1-6). While there are a number of 7-*endo* cyclizations that have been reported, 6-*exo* cyclizations tend to be more common.³⁸⁻⁴⁰ The 6-*exo* cyclizations have not been modeled as extensively as 5-*exo* cyclizations. Usually, 6-*exo* cyclizations are slower than the 5-*exo* counterpart, and in some cases, hydrogen transfer and 7-*endo* can compete.¹¹

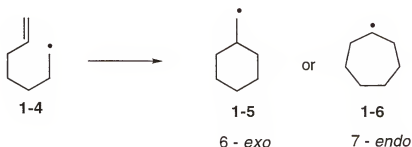


Figure 1-6. Cyclization of the 7-heptenyl radical (1-4) to give the cyclohexylcarbinyl (1-5) or the cycloheptenyl (1-6) radical.



Figure 1-7. Cyclization of the pentenyl radical (**1-7**) to give the cyclobutylcarbiny radical, **1-8**.

Another type of radical cyclization is that of pentenyl radicals. These cyclize in a 4-*exo*⁴¹⁻⁴³ or 5-*endo*⁴⁴ manner, neither of which is common. The stereoelectronically preferred mode of cyclization is the 4-*exo* pathway (Figure 1-7) which, with the right substituents, can be rapid enough to be synthetically useful.⁴¹ These cyclizations are often reversible with the *n*-pentenyl radical (**1-7**) being favored at equilibrium over the closed cyclobutylcarbiny radical, **1-8**.

Determination of Organic Radical Kinetics

The rates of radical reactions may be determined by either direct or indirect methods. One very popular mode of direct rate determination is that of Laser Flash Photolysis (LFP). In this method, which has been discussed at length in the literature,⁴⁵ radicals are generated by a laser pulse of appropriate wavelength from precursors possessing a suitable chromophore. Some of the precursors used in this method include alkyl iodides, diacyl peroxides and *O*-acylthiohydroxamic esters of Barton *et al* (Figure 1-8).⁴⁶

Once generated, these radicals usually undergo either unimolecular or bimolecular alkene addition to an aryl-substituted double bond. The formation of the newly formed radical (Figure 1-9) is monitored in a time dependent manner by UV-visible spectroscopy by observing the increase in the characteristic absorption of the benzyl radical ($\lambda_{\text{max}} \sim 320\text{nm}$). The

experimental growth curve for bimolecular additions is fit to the expression Equation 1-12 which gives the absolute rate of addition, k_{add} .

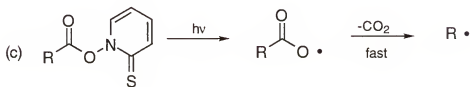
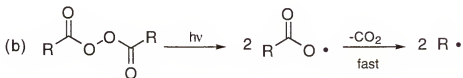
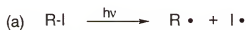


Figure 1-8. Laser flash photolytic generation of radicals $\text{R} \cdot$ from (a) iodide, (b) peroxide, and (c) O-acylthiohydroxamic ester precursors.

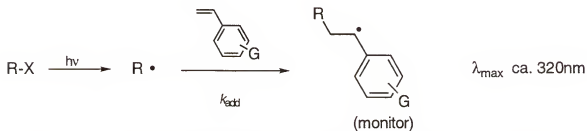


Figure 1-9. LFP generation of $\text{R} \cdot$ and detection of the transient benzyl radical adduct for determination of the absolute rate of addition, k_{add} .

$$k_{\text{obs}} = k_o + k_{\text{add}} [\text{alkene}] \quad (1-12)$$

In the event the radical intermediate partitions between two competing pathways, the rates of reaction may be determined indirectly by competition kinetics. In this method, the rate of one of the processes is known and it may be used to determine the rate of the competing process. This involves the analysis of the products by either spectroscopic or chromatographic techniques upon completion of the reaction. The competition is usually between two bimolecular processes (Figure 1-10), or between a bimolecular and a unimolecular process (Figure 1-11).

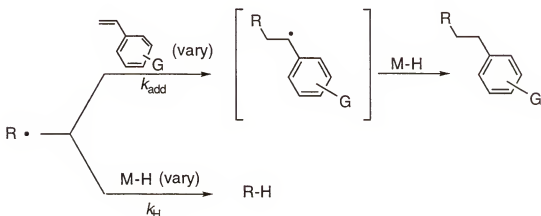


Figure 1-10. Competition between bimolecular addition to an alkene and hydrogen abstraction to get k_{add} and k_H , respectively.

In the case where there is competition between two bimolecular processes, the experiment is conducted so that there are two trapping agents, that is, an olefin (for example, styrene) and a hydrogen atom donor (Figure 1-10). Both trapping agents are present in large excess so as to ensure pseudo-first order conditions. Once the radical is generated, it may undergo addition to the styrene, for which the rate constant, k_{add} , is known, to form a benzylic radical. This radical is trapped in turn by abstracting a hydrogen atom from the radical

reducing agent. The rate for trapping of the benzylic radical is considered to be unimportant *if the addition reaction is irreversible*.

Alternatively, the radical may be trapped immediately by the hydrogen atom donor with a rate constant k_H . The value of k_H may be determined by using Equation 1-13 where [reduced] and [adduct] are the final product concentration, [M-H] is the concentration of the hydrogen atom donor, and $[CH_2=CHR']$ is the concentration of the olefin. In order to ensure that the kinetic measurements are accurate, a series of experiments is carried out where the concentrations of the trapping agents are varied.

$$\frac{[\text{reduced}]}{[\text{adduct}]} = \frac{[k_H] [R\cdot] [M-H]}{[k_{\text{add}}] [R\cdot] [CH_2=CHR']}] \quad (1-13)$$

Rates of cyclization may be determined in a similar manner. With the rate of hydrogen abstraction, k_H , known, competition experiments may be performed where the unimolecular addition process competes with the bimolecular hydrogen abstraction (Figure 1-11). The ratio of products, that is, cyclized products vs. hydrogen abstraction products, are obtained from the pseudo-first order relation in Equation 1-14.

$$\frac{[\text{reduced}]}{[\text{cyclized}]} = \frac{[k_H] [R\cdot] [M-H]}{[k_{\text{cycl}}] [R\cdot]} \quad (1-14)$$

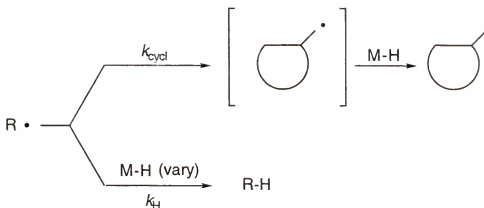


Figure 1-11. Competition between unimolecular alkene addition and bimolecular hydrogen abstraction to obtain k_{cycl} and k_H , respectively.

It is important to note that in order to obtain reliable kinetic data, the radical chain reaction should be very efficient with high conversions of the precursors. This is especially crucial when using indirect methods since they depend a great deal on the "mass balance" of the reaction. Ideally, conversions of 90% or better are desired.

1.3 Overview of Solvolytic Displacement Reactions

Nucleophilic substitution reactions have also been studied extensively by organic chemists. While many recognized the synthetic benefit of these reactions, and even made individual observations, it was not until the 1930's that these reactions were characterized. In kinetic experiments on nucleophilic substitutions of quaternary ammonium salts, Hughes, Ingold and Patel⁴⁷ found that two different mechanisms were involved depending on the ammonium salt used. Although the rates of all reactions were first order in the quaternary ammonium ion, some of the reactions were first order in the concentration of the

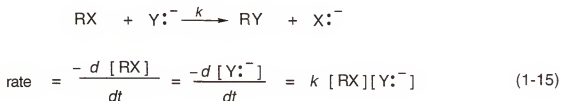
nucleophile while others were independent in the concentrations of the nucleophile.

Substitution by Direct Displacement



Figure 1-12. Nucleophilic displacement of hydroxide on trimethyl-*n*-decylammonium salt to give methanol and dimethyl-*n*-decylamine.

Figure 1-12 shows the reaction between hydroxide ion and trimethyl-*n*-decylammonium cation. This is an example of a reaction studied by Hughes, Ingold and Patel where the reaction is dependent on the concentration of the nucleophile.⁴⁸ The overall rate is second order, that is, first order in both the nucleophile and in the ammonium salt. The reaction occurs by a direct displacement mechanism which is concerted. For this reason, the reaction is called an S_N2 (substitution, bimolecular, nucleophilic) reaction. The rate expression for this bimolecular process is shown in Equation 1-15.



While the S_N2 has a single, rate-determining transition state, it does not have an intermediate. The mechanism involves the "backside" attack of the nucleophile (that is, the side opposite to that of the leaving group) with the

simultaneous bond cleavage between the carbon atom and the leaving group. The transition state involves a pentacoordinate carbon that has a trigonal bipyramidal geometry where the nucleophile and the leaving group are both coordinated to the central carbon. The reaction occurs with inversion of configuration. Figure 1-13 shows the potential energy diagram for the direct displacement reaction.

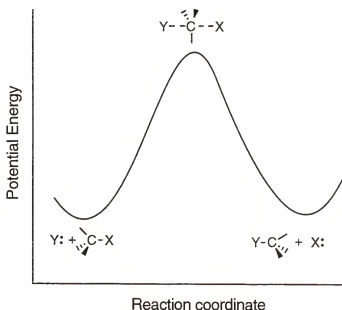


Figure 1-13. Potential diagram for an S_N2 reaction

From the Frontier Molecular Orbital (FMO) approach, the frontier orbitals involved include the orbital of the nucleophile, Y, which is a filled lone pair orbital, and a σ^* antibonding orbital associated with the carbon undergoing substitution and the leaving group, X. Backside attack is favored because the strongest initial interaction will be between the filled orbital of the nucleophile and the σ^* orbital, which has a large lobe on the carbon directed away from the C-X bond (Figure 1-14).⁴⁹



Figure 1-14. FMO depiction of backside nucleophilic attack.

In general, the decreasing order of reactivities of alkyl halides toward the same nucleophile is as follows:^{50, 51}



The less basic groups are usually the better leaving groups. The decreasing order of the effect of alkyl group structure on $\text{S}_{\text{N}}2$ reactions is:⁵⁰



In other words, increasing the number of substituents makes it more difficult for the nucleophile to come within bonding distance of the carbon bearing the leaving group. This means that the nucleophile must have enough energy to overcome the nonbonding interactions and actually attack the carbon where the substitution occurs.

Substitution by Ionization

Hughes, Ingold and Patel also found that when hydroxide ion was reacted with (diphenylmethyl)tri-methylammonium cation, the rate of the reaction was independent of the concentration of the nucleophile (Figure 1-15).⁴⁸ The rate is first order overall and depends only on the ammonium ion concentration. Based on this and similar experiments, they realized that those substitutions, where the rates are independent of the concentration of the nucleophile, are on hindered substrates capable of forming stable carbocations.

The reaction depicted in Figure 1-15 proceeds by an ionization mechanism where the rate determining step is the heterolytic cleavage of the reactant giving a tricoordinate carbocation and the leaving group. Once the

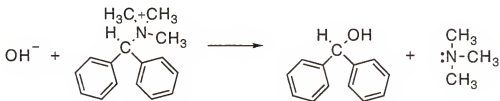


Figure 1-14. Nucleophilic displacement of hydroxide ion on (diphenyl)trimethylammonium cation to give benzyhydrol and trimethylamine.

dissociation occurs, there is a rapid combination of the highly electrophilic carbocation with the base present in the reaction medium. Figure 1-16 shows the potential energy diagram of nucleophilic substitution reactions by the ionization mechanism.

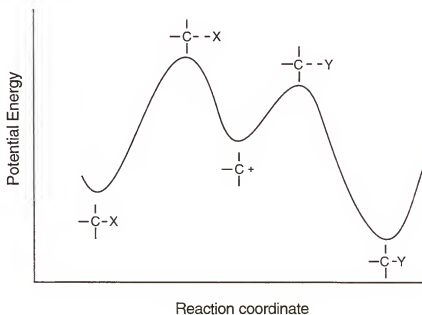
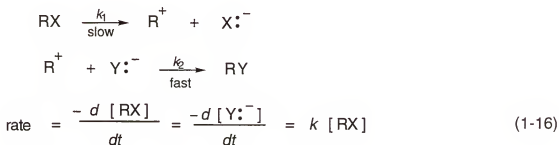


Figure 1-16. Potential energy diagram for the nucleophilic substitution reaction by the ionization mechanism.

The fact that the dissociation is rate-determining explains why the rate is independent of the concentration of the nucleophile. This reaction and those following the same reaction mechanism are called S_N1 (substitution, nucleophilic, unimolecular) reactions. The rate expression for the S_N1 reaction is therefore:



Based on Hammond's Postulate, for the S_N1 reaction pathway, the transition state should resemble the product of the first step, that is, the carbocation intermediate. The rate-determining step, k_1 , will be enhanced by factors that either raise the energy of the reactant or lower the energy of the carbocation. Solvent polarity is one factor that affects ionization reaction rates. Solvents with high dielectric constants will lower the transition state energy more than solvents that are less polar. Less polar solvents should enhance the ionization of cationic substrates since there is a dispersal of charge in the transition state.

Similarly, electronic and steric effects will also affect the reaction rates of the ionization process. Stabilization of the carbocation by electron release and the ability of the leaving group to accept the electron pair from the covalent bond of the reactant are the most important electronic effects. During ionization, the three remaining groups are spread apart so that steric compression by the

bulky groups favor the ionization. Therefore, the decreasing order of reactivity for S_N1 reactions is:



In general, S_N1 reactions occur with a predominance of racemization.

Nucleophilicity

The effect of a Lewis base on the rate of a nucleophilic substitution reaction is generally referred to *nucleophilicity*. In contrast, *basicity* refers to the position of an equilibrium reaction with a proton, or some other acid. While there are no absolute scales to quantify nucleophilicity or basicity, there are certain general trends for both.⁵² Factors influencing nucleophilicity have been assessed in the context of S_N2 reactions since these reactions are dependent on the nature of the nucleophile. S_N1 reactions however, are not affected by nucleophiles and therefore, the effect of nucleophilicity will not be evident in the rates of these unimolecular reactions. The nature of the nucleophile will only affect the product distribution from the partitioning of the carbocation intermediates among the available pathways.

The factors that affect nucleophilicity include: (1) the solvation energy of the nucleophile; (2) the strength of the bond being formed to carbon; (3) the size of the nucleophile; (4) the electronegativity of the attacking atom; and the polarizability of the attacking atom.^{50(a)}

Nucleophilicity does not correlate directly with basicity. While azide ion, phenoxide ion, and bromide have widely divergent basicities, they are all equivalent in nucleophilicity.⁵³ On the other hand, azide ion and acetate ion are nearly identical in basicity but azide ion is more nucleophilic. Nucleophilicity decreases going across a row in the periodic table. For example, $\text{HO}^- > \text{F}^-$, and $\text{C}_6\text{F}_5\text{S}^- > \text{Cl}^-$. This order is primarily determined by

electronegativity. Conversely, nucleophilicity increases going down the periodic table, for example, $I^- > Br^- > Cl^-$. The increase is due to the decrease in electronegativity while going down the periodic table, the greater polarizability and the weaker solvation of the heavier atoms.

Determination of the Rates of Substitution Reaction

There are two main methods for determining how the rates of reactions depend on the concentration of the reacting substances. They are the differential method and the integration method.⁵³ In the differential method, the rates are measured directly by determining the slopes of concentration-time curves, and analyzing the manner in which the slopes depend on the concentration of the reactants. In the method of integration, a tentative decision is made as to the order of the reaction. The differential equation pertaining to that order is then integrated resulting in an expression for concentration as a function of time. If the right order has been chosen, this will be indicated by good correlation of the results with the equation. If the results do not correlate well, then another order must be chosen. For the experiments described in Chapter 3, the integration method was used. Detailed discussions for both the differential and integration methods are found in the literature.⁴⁴

CHAPTER 2

REACTIONS OF α -AMMONIO DISTONIC RADICAL CATIONS

2.1 Introduction

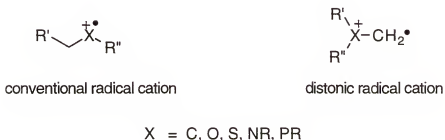


Figure 2-1. Representation of conventional radical cations and distonic radical cations.

In 1984, the term "distonic ion" was introduced by Yates, Bouma and Radom⁵⁴ to describe ions having separated charged and radical sites. Greek letters are used to designate the relative location of the charge and radical sites. For example, a radical site that is adjacent to a charged site is called an α -distonic radical cation, as depicted in Figure 2-1. Theoretical and experimental studies have shown that these species may be more thermodynamically and kinetically stable than their conventional counterparts (Figure 2-1).⁵⁴⁻⁵⁶ Distonic radical cations play an important role as the central intermediates in the dissociation reactions of many ionized molecules and have been produced from certain X- or γ -ray irradiated amino acids.⁵⁷ It is therefore believed that

investigating the reactivity of distonic ions may lead to a better understanding of the biological consequences of ionizing irradiation.

Although distonic radical cations have been accepted as common and stable gas phase intermediates, very little is known about them. Their chemical properties have been based almost entirely on gas phase unimolecular reactions of excited ions.⁵⁸ It has been shown that distonic radical cations like $(\text{CH}_3)_2\text{S}^+\text{CH}_2^\bullet$, exhibit gas phase reactivity including hydrogen abstraction and alkene addition,^{59,60} behavior that is consistent with that of a typical carbon-centered radical. These species have therefore been described as having the characteristics of "reactive radical(s) with an inert charged site."⁵⁹

2.2 Overview of Reported Studies In Solution

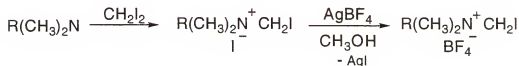


Figure 2-2. Synthesis of Iodomethylammonium salts, precursors of distonic radical cations

Recognizing the potentially unique nature of these radicals, Dolbier and co-workers initiated a systematic, quantitative study of distonic radical cations in solution.⁶¹ The prototypical α -ammoniomethyl radical system, $\text{R}(\text{CH}_3)_2\text{N}^+\text{CH}_2^\bullet$, was examined first. These radicals were generated from their readily synthesized iodomethyl precursors⁶¹ (Figure 2-2) by means of irradiative free radical initiation (Figure 2-3).

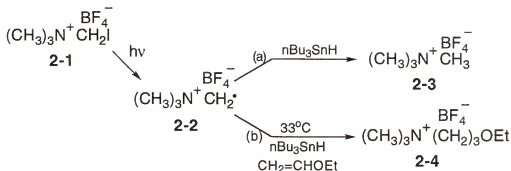


Figure 2-3. Reactivity of distonic radical **2-2** in solution: (a) reduction with tributyltin hydride; (b) intermolecular alkene addition with ethyl vinyl ether.

The fact that the trimethyliodomethyl salt, **2-1**, in the presence of tributyltin hydride was observed to undergo rapid light-induced conversion to the tetramethylammonium salt, **2-3**, was evidence that the reaction was that of a well-behaved free radical chain process involving **2-2**. No competitive bimolecular addition of **2-2** to styrene, α -methylstyrene, pentafluorostyrene or 1-hexene was observed however. In fact, the only case where bimolecular addition involving **2-2** was observed was when **2-1** was reacted with ethyl vinyl ether to produce **2-4** (Figure 2-3(a)).

Dolbier and co-workers reported that while minimal intermolecular alkene addition was exhibited by **2-2**, intramolecular alkene addition occurred quite readily for **2-5** and **2-6** (Figure 2-4). Cyclization of **2-5** to give the 5-exo radical cyclized product (**2-6**) was so fast that no competitive reduction could be observed at the maximum possible concentration of tributyltin hydride (0.18M) in 1:1 CD₃OD/C₆D₆. They concluded that kinetic examination of 5-exo cyclizations would not be possible by either LFP or competition methodology based on this result, and the fact that **2-7** cyclized too fast to be measured by nanosecond LFP ($k_C \geq 10^8 \text{ s}^{-1}$ at 25°C).

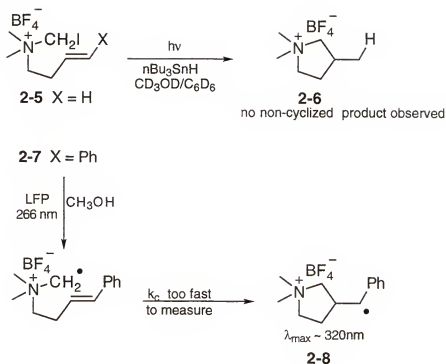


Figure 2-4. Results from 5-exo cyclization studies with **2-5** and **2-7**.

As there is an approximate 100-fold decrease for 6-exo versus 5-exo radical cyclizations,⁶² the 7-heptenyl analogs were synthesized and studied. The 7,7-biphenyl system, **2-9**, produced excellent kinetic results when studied by LFP over a temperature range of -60°C to +20°C.⁸ Arrhenius parameters were then derived from the kinetic data (Figure 2-5). The rate of cyclization for **2-9** was found to be $3.0(\pm 0.4) \times 10^7 \text{ s}^{-1}$ at 25°C, almost 60 times faster than the related 7,7-biphenyl-6-heptenyl radical ($k_{\text{C}} = 5 \times 10^5 \text{ s}^{-1}$).⁶³

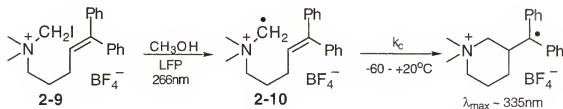


Figure 2-5. Cyclization reaction of **2-10** monitored by LFP; $\log A = 10.5 (\pm 0.3)$, $E_{\text{a}} = 4.1 (\pm 0.5) \text{ kcal mol}^{-1}$, $k_{\text{C}} = 3.0 (\pm 0.4) \times 10^7 \text{ s}^{-1}$ at 25°C.

By performing a series of competitive kinetic experiments, the rate of hydrogen abstraction from tributyltin hydride could then be obtained using **2-9** as a radical clock (Figure 2-6). From those experiments, the rate of hydrogen abstraction from tributyltin hydride was found to be $7.2(\pm 1.5) \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ at 33°C , a rate constant that is slightly enhanced when compared to the rate of H-transfer from tributyltin hydride to a primary alkyl radical.²¹

$$\frac{[\text{RED}]}{[\text{CYC}]} = \frac{k_{\text{H}}[\text{nBu}_3\text{SnH}]}{k_{\text{C}}} \quad \text{Equation 2-1}$$

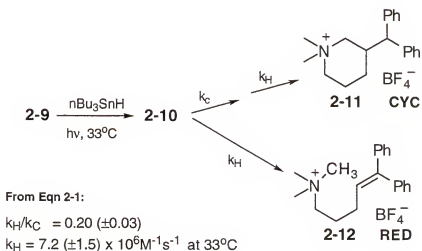


Figure 2-6. Competition of **2-10** to give directly reduced product and cyclized product.

Competitive cyclization and reduction studies of the monophenyl (**2-13**) and unsubstituted (**2-15**) systems were then performed since the rate constant

for hydrogen abstraction from tributyltin hydride was available. The rate constant for the cyclization of **2-13** determined to be $1.7 \times 10^7 \text{ s}^{-1}$ at 25°C while that of **2-15** at 33°C was observed to be $1.5 \times 10^6 \text{ s}^{-1}$ (Figure 2-7), almost 200 times faster than the rate for the analogous 6-exo cyclization of the 6-heptenyl radical ($7.6 \times 10^3 \text{ s}^{-1}$).⁶²

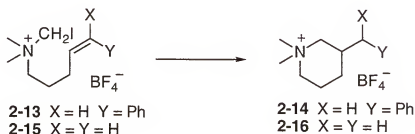


Figure 2-7. Cyclization of **2-13** and **2-15**; k_c for **2-13** = $1.7 \times 10^7 \text{ s}^{-1}$ at 25°C , k_c for **2-15** = $1.5 \times 10^6 \text{ s}^{-1}$.

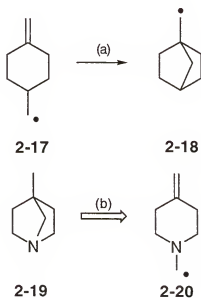


Figure 2-8. Modified 5-hexenyl radical cyclizations to give bicyclic products; (a) irreversible ring closure that has been utilized in synthesizing numerous bridgehead-substituted bicyclo[2.2.1]heptanes; (b) **2-19** is targeted by using methodology similar to (a).

It is worth noting that Della and Knill have been able to utilize these very reactive ammonio distonic radical cations in the syntheses of novel heterocycles.⁶⁴ Knowing that the modified 5-hexenyl radical **2-17** has been shown to undergo smooth transformation to **2-18**,^{64a} they purposed to take advantage of the rearrangement in preparing the 1-azabicyclo[2.2.1]heptyl system (**2-19**) via the corresponding intermediate radical, **2-20** (Figure 2-8). They were faced with a predicament however, when Padwa and co-workers reported that the 2-aza-2-benzylhex-5-enyl radical, **2-22**, is rapidly trapped by tributyltin hydride to give only the reduced product, **2-23** (Figure 2-9).⁶⁶ Realizing that the stabilizing influence of the heteroatom on the adjacent electron-deficient center could be removed effectively by quaternizing the nitrogen, they synthesized the iodomethyl salt, **2-24**, and were able to accomplish the desired cyclization to get **2-26** (Figure 2-10). None of the directly reduced product, **2-27**, was detected.

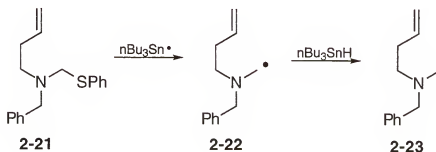


Figure 2-9. Results from treating 2-aza-2-benzylhex-5-enyl radical with nBu_3SnH .

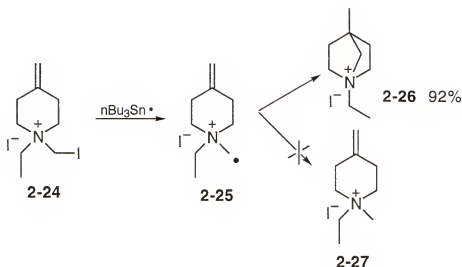


Figure 2-10. Example where distonic radical cation is used to synthesize bridgehead nitrogen heterocycles.

Hammitt Studies

As mentioned earlier, gas phase studies have shown that distonic radical cations behave like electrophilic alkyl radicals with an inert charge site.⁵⁹ Dolbier and co-workers purposed to determine the extent of the "electrophilicity" of these species as a function of the general molecular environment of the charged and radical sites.⁷¹ In their case, they determined to perform experiments in solution.

In their earlier work,⁶¹ Dolbier and co-workers successfully showed by competition studies (cyclization vs. reduction) that α -ammonio distonic radical cations exhibit behavior that is consistent with other carbon-based radicals. These species are however, somewhat more reactive than analogous hydrocarbon radicals in both the cyclization and reduction processes. While no direct evidence for the electrophilic character of distonic radicals was provided from the studies, there remained a possibility that the enhancement in the

reactivity could be partly due to the expected electrophilic character of these species. To investigate this possibility, they performed a Hammett study on a series of *p*-substituted N,N-dimethyl-N-iodomethyl-5-aryl-4-pentenaminium salts (Figure 2-11).

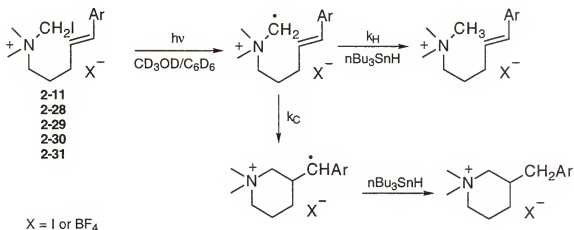


Figure 2-11. Hammett study for the cyclizations of *p*-substituted N,N-dimethyl-N-(5-aryl-4-pentenyl)methanaminium-1-yl radicals.

In the Hammett study, photo-induced free radical chain competition experiments were performed which involved competition between cyclization and reduction of the intermediate radicals of 2-11, 2-28, 2-29, 2-30 and 2-31.⁷¹ For each member of the series, six samples of substrate and tributyltin hydride in a mixture of methanol- d_4 and benzene- d_6 were prepared in sealed NMR tubes varying only in the concentration of the tin hydride. After irradiating the samples for 45min at 33°C in a Rayonet reactor, the ratios of the reduced products to the cyclized products were determined by 500MHz proton NMR spectroscopy, using anisole as an internal standard. When a plot of these ratios were made against the changing concentration of the tin hydride, the slope of the lines gave the ratio k_H/k_C , and since the value for k_H was known, k_C could

be determined for each system. The results from that study is shown in Table 2-1.

Table 2-1. Rate constants for cyclization of *p*-substituted N,N-dimethyl-N-(5-aryl-4-pentenyl)methanaminium-1-yl radicals⁷¹

Substrate	2-28	2-29	2-11	2-30	2-31
<i>p</i> -Substituent	CF ₃	Cl	H	CH ₃	OCH ₃
σ^+	0.61	0.11	0	-0.31	-0.78
k_H/k_C	0.35	0.28	0.27	0.22	0.13
$k_C(\times 10^7 \text{s}^{-1})$	2.1	2.5	2.6	3.2	5.5

The Hammett plot gave best correlation when using σ^+ rather than when σ or $\sigma^\bullet$ was used. A good correlation with σ^+ indicated that there was conjugative interaction of the *p*-substituent with the reaction site. The slope of the Hammett plot, ρ , was -0.29 indicating that there is delocalization to an electron deficient-site. The transition state for the cyclization of this electrophilic radical should therefore be early with significant polarization, but with little radical character developed at the benzylic site (Figure 2-12).

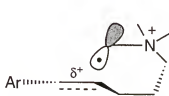


Figure 2-12. Depiction of the cyclization transition state

Pyridinio Distonic Radical Cation

Based on the observation that the trimethylammonio radical, **2-2**, was quite reluctant to add bimolecularly to electron rich alkenes while the 7, 7 biphenylheptenyl-substituted radical, **2-10**, and similar radicals performed rapid unimolecular alkene addition, it seemed likely that **2-2** might be too sterically hindered (due to the presence of the methyl groups) to add to olefins. We then thought it logical to design an ammonio system that had tethered alkyl groups, and attempt to add it to various olefins. In the event that a less sterically hindered distonic radical cation (such as a pyridinium substituted radical) performed such alkene additions, it could be concluded that prior reactions involving **2-2** were inhibited by steric hindrance.

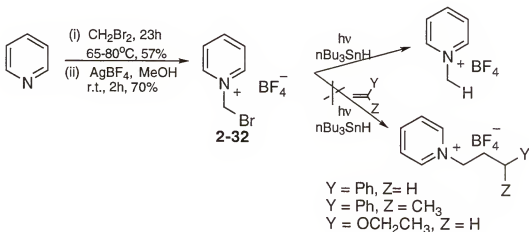


Figure 2-13. Reactivity of pyridinium system

It was very apparent that a methylene pyridinio distonic radical cation might not perform facile intermolecular additions to alkenes due to the stabilization of the radical through resonance. Nevertheless, with literature precedent for the addition of a benzylic radical adding to substituted olefins

such as α -methylstyrene,⁶⁷ we attempted to do the same with the pyridinium analog, which would have similar resonance stabilization.

The pyridinio distonic radical cation was generated from the readily synthesized pyridinium tetrafluoroborate salt, **2-32**⁶⁸, by reacting pyridine with a six-fold excess of dibromomethane. In this reaction, the bis-pyridinium salt was also formed as a minor product and was successfully removed by recrystallization from acetonitrile. Once the radical was generated, it was quickly reduced by tributyltin hydride (Figure 2-13). Again, no bimolecular addition to olefins was observed.⁶⁹

2.3 Cleavage Studies of Benzyl-Substituted Ammonium Salt

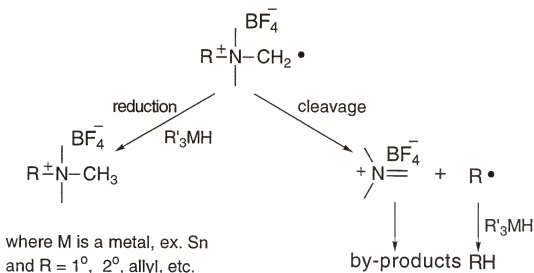


Figure 2-14. Study of the cleavage of distonic radical cations in competition with reduction.

In an attempt to explore a variety of possible reactions involving α -ammonio distonic radical cations, investigations into cleavage reactions were also initiated. The intent of this particular study was to design a number of alkyl dimethylmethylene distonic species where the alkyl group would be primary, allyl, and so on (Figure 2-14), observe any cleavage reactions that might occur in solution, and determine conditions whereby rates could be obtained for the competition of cleavage versus direct reduction.

At first, we attempted to induce cleavage in butyldimethyl-iodomethyl ammonium tetrafluoroborate; however, our attempts were unsuccessful since the resulting butyl radical, primary in nature, was reluctant to form. A benzylic substituent was then chosen because a more stable benzyl radical would be more likely to be formed in the desired cleavage process.

Surprisingly, when the typical methodology for synthesizing our iodomethyl ammonium precursor⁶⁸ was employed in an attempt to obtain **2-33**, only **2-34** was isolated from the reaction (Figure 2-15). The mechanism by which this curious result was obtained is discussed in detail in Chapter 3.

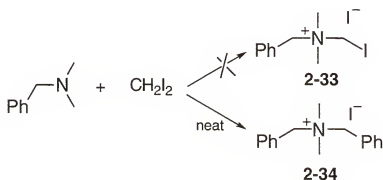


Figure 2-15. Attempt to synthesize benzyliodomethyl salt for cleavage study.

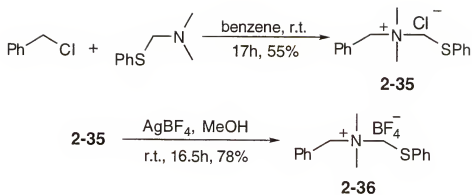
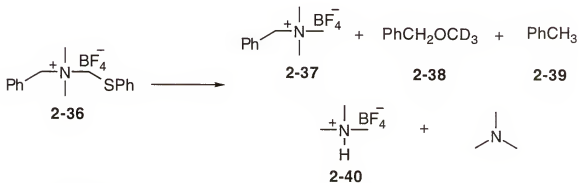


Figure 2-16. Synthesis of thiophenyl ether precursor **2-36** for generation of benzyl substituted ammonio dicationic radical.



Conditions

	2-37	:	2-38	:	2-39	:	2-40
3eq n-Bu ₃ SnH, C ₆ D ₆ /CD ₃ OD hv, 25°C, 3h	10	:	20	:	15	:	55
9eq nBu ₃ SnH, C ₆ D ₆ /CD ₃ OD hv, 25°C, 3h	9	:	16	:	27	:	48
3eq nBu ₃ SnH, C ₆ D ₆ /CD ₃ OD AIBN, Δ, (85°C), 1h	94	:	0	:	6	:	0

Figure 2-17. Results from reacting **2-36** with tributyltin hydride.

Based on literature precedent for generating radicals from thiophenoxy precursors,⁶⁴ the benzyl-substituted distonic radical was generated from **2-36** which was synthesized as described in Figure 2-16.⁶⁵ Irradiating **2-36** in the presence of tributyltin hydride, which was added to the reaction mixture slowly, gave the expected reduction product **2-37**, as well as products from competing cleavage reactions. (Figure 2-17). As expected, toluene was detected in the reaction mixture by proton NMR analysis and mass spectral analysis. The byproducts from the decomposition of the iminium salt were detected as trimethylamine and trimethylammonium salt. These products were confirmed by adding authentic samples to the reaction and observing peak growth in the proton NMR spectra. They were also identified by mass spectral analysis.

Surprisingly, with an increase in the concentration of tin hydride under ultraviolet irradiation, there was no increase in the formation of the directly reduced product, **2-37**. This observation coupled with the fact that **2-38** was formed in the reaction mixture suggested that the substrate was not being consumed by a simple radical mechanism.

The reaction mechanism was partly explained when **2-37**, which was synthesized independently by reacting N,N-dimethyl-N-benzylamine with trimethyloxonium tetrafluoroborate, was irradiated in the presence of tributyltin hydride. The products from the reaction were **2-38**, **2-39**, **2-40** (Figure 2-18), the same products formed during the irradiation of **2-36**. The products are the result of competing heterolytic and homolytic cleavages (discussed in more detail in Section 2-8) When the same reaction was performed under thermal initiative conditions where AIBN was used as a radical initiator, no cleavage of **2-37** was detected. In fact, when the reaction mixture was heated at 80°C for 10h, no reaction was detected. (**Note** While the photolytic reaction of **2-37** was well-behaved, no additional kinetic studies were performed since our

purpose was generate α -ammonio distonic radicals of the type $R_3N^+CH_2\cdot$ and observe their subsequent reactions.)

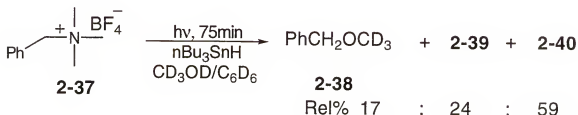


Figure 2-18. Photochemically induced cleavage of **2-37**.

When **2-36** was subjected to thermal initiative conditions, the only products detected appeared to come from a radical intermediate as there was no sign of the methylbenzylether, **2-38**, the distinguishing product from heterolytic cleavage. While the thermal reaction proceeded via a radical mechanism, it did not carry a chain very well since a significant amount of starting material was recovered in the product mixture, that is, 26% of the product mixture.

2.4 Allyl Substituted Ammonio Distonic Radical

Our quest to thoroughly investigate the full scope of reactivity of distonic radical cations continued as we turned our attention to the allyl substituted ammonio radical. The iodomethyl salt precursor (**2-41**) was synthesized in low yield when allyldimethylamine was reacted with diiodomethane (Figure 2-19).

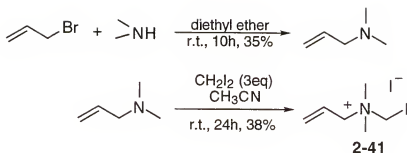
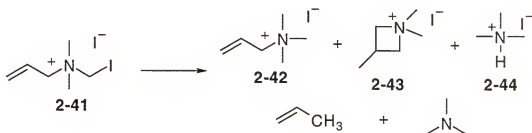


Figure 2-19. Synthesis of allyl-substituted ammonium salt.

It was quite interesting to note that when the salt **2-41** was irradiated in the presence of tributyltin hydride, products from three types of radical reactions were observed. As expected, allyltrimethyl ammonium iodide, **2-42**, was formed from the direct reduction of the initially formed distonic radical. Propene and trimethyl ammonium iodide (**2-43**), products due to homolytic cleavage, were also detected by proton NMR and mass spectral analysis. The formation of these products were also expected since a cleavage reaction was observed for the benzylic system, **2-36**. No products from heterolytic cleavage, that is, allylmethylether, were detected.

The product of major interest came in the form of the azetidinium salt, **2-43**. The formation of the azetidinium salt was detected by two dimensional proton NMR and mass spectral analyses. When tributyltin hydride was added slowly to **2-41** under photochemical conditions, **2-43** was formed as only 27% of the product mixture (Figure 2-20). The amount of **2-43** decreased with respect to cleavage products when the reaction was repeated under thermolytic conditions. With *tris*(trimethylsilyl)silane, a radical reducing agent that is approximately ten times slower than tributyltin hydride in its ability to reduce radicals,⁷⁰ the amount of **2-43** in the product mixture increased to 53%. It should be noted that in all cases, the reactions went to completion with no signs

of the starting material in the product mixture. This was strong evidence that an efficient free radical chain mechanism was involved.



Conditions	2-42	:	2-43	:	2-44
1.5eq n-Bu ₃ SnH, C ₆ D ₆ /CD ₃ OD hv, 25°C, 50min	70	:	27	:	3
1.5eq nBu ₃ SnH, C ₆ D ₆ /CD ₃ OD Δ, (85°C), AIBN, 55min	70	:	19	:	12
1.5eq (TMS) ₃ SiH, C ₆ D ₆ /CD ₃ OD hv, 25°C, 120min	37	:	53	:	10

Figure 2-20. Radical reactions of **2-41** with nBu₃SnH and (TMS)₃SiH.

In the experiments where tributyltin hydride was used, the amount of reduced product was predominant with only one and a half equivalents of the tin reagent. It should be noted that for competitive kinetic experiments, the radical reducing agent would have to be at least in ten-fold excess in order to ensure pseudo-first order conditions. An increase in the concentration of tin hydride would cause an increase in the amount of **2-42** (Equation 2-1) and no competing cleavage or cyclization would have been observed.

From the data shown in Figure 2-20, it was clear that the best radical reducing agent for obtaining competitive kinetic data was

tris(trimethylsilyl)silane). It was therefore necessary to obtain a rate of hydrogen atom abstraction for α -ammonio distonic radical cations from *tris*(trimethylsilyl)silane. For this purpose, it would be necessary to perform further competitive kinetic experiments using either 2-9, 2-13 or 2-15 with *tris*(trimethylsilyl)silane, or another radical reducing agent with similar reactivity.

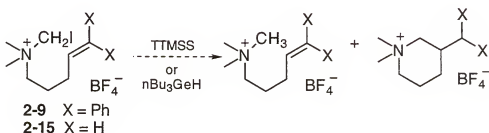


Figure 2-21. Attempt to get H-atom abstraction rates from $n\text{Bu}_3\text{GeH}$ and TTMSS.

When we attempted to react both 2-9 and 2-15 with a tenfold excess of *tris*(trimethylsilyl)silane, we did not observe the competition described in Figure 2-21. Instead, we saw multiple products, the major product being the cyclization product. None of the reduced product was detected. This indicated that the reaction conditions were not suitable for a kinetic study. Assuming that the presence of a silyl group was problematic to the reaction conditions, that is, silyl adding to the olefin, the reactions were repeated using tributylgermanium hydride which reduces alkyl radicals about four times slower than *tris*(trimethylsilyl)silane. Again, no competition between the cyclization and reduction pathways were observed, and as a result, no rate constants for the hydrogen atom abstraction from *tris*(trimethylsilyl)silane and tributylgermanium hydride were obtained by competitive kinetics.

2.5 Kinetic Isotope Effect Study

Knowing that isotopic substitution has been proven to be very valuable in the study of reaction mechanism, we decided to study the kinetic isotope effect of the reduction of the ammonio-substituted reactive intermediate. For this study, experiments were performed where a distonic radical cation precursor would be reacted with a trialkylmetal hydride and its corresponding deuteride. The relative rates for both hydrogen and deuterium abstractions were then compared in order to obtain a value for the kinetic isotope effect. All experiments were executed in an oxygen-free atmosphere in sealed pyrex NMR tubes. Again, a mixture of deuterated solvents, methanol and benzene, were used. The reaction mixtures were subjected to ultraviolet photolysis in a Rayonet reactor (254nm lamps). Reaction mixtures were analyzed by mass spectral analysis of the isolated salt mixtures.

Average Kinetic Isotope Effect Study

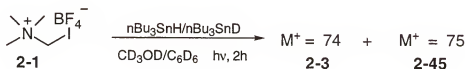


Figure 2-22. Competitive reduction of 2-1 with nBu₃SnH and nBu₃SnD.

In order to determine the kinetic isotopic effect for the reduction of 2-1 (Figure 2-22), a standard concentration of 2-1 was reacted with tributyltin hydride and tributyltin deuteride of varying concentrations. Six pyrex NMR tubes were filled with 600μL portions of a 20.2mM stock solution of 2-1 in a 1:1 mixture of deuterated methanol and deuterated benzene. The amounts of

tributyltin hydride and tributyltin deuteride placed in each tube are shown in Table 2-2.

Table 2-2. Varying amounts of $n\text{Bu}_3\text{SnH}$ and $n\text{Bu}_3\text{SnD}$ used in experiment for determining average kinetic isotope effect.

Tube #	Vol $n\text{Bu}_3\text{SnH}$ (μl)	Vol $n\text{Bu}_3\text{SnD}$ (μl)
1	60	40
2	55	45
3	50	50
4	45	55
5	40	60
6	35	65

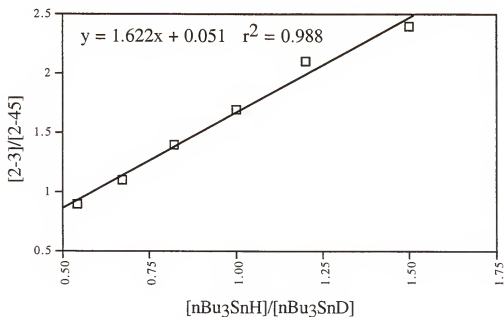


Figure 2-23. Plot of ratios of products (2-3/2-45) against ratios of radical reducing agents. The average kinetic isotope effect is the slope = 1.62 (± 0.09).

After irradiating the tubes for 1.5h, the volatiles were removed from the reaction mixtures and the non-volatiles were analysed by mass spectral analysis. The relative abundance of $M^+ 74$ (**2-3**) and M^+75 (**2-45**) were observed for each tube. The ratios of these products were plotted as a function of the ratio of the concentrations of both radical reducing reagents (Figure 2-23). The average kinetic isotope effect was the slope of the plot and was found to be 1.62 (± 0.09).

Table 2-3 Data for calculating individual kinetic isotope effect.

[2-3]/[nBu ₃ SnH]	[2-45]/[nBu ₃ SnD]	KIE ^(a)
1.2	0.73	1.64
1.2	0.71	1.69
1.3	0.74	1.76
1.3	0.77	1.69
1.3	0.81	1.60
1.3	0.82	1.59

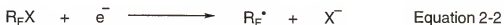
^(a) Average kinetic isotope effect = 1.66

Using the same data that was applied to Figure 2-23, kinetic isotope effects were calculated for each tube (Table 2-3). The ratio of the concentration of **2-3** to the volume of tributyltin hydride used was obtained for each tube. The same thing was done for **2-45** and tributyltin deuteride. It was observed that the rate of reduction with tributyltin hydride stayed relatively constant while the rate of reduction with tributyltin deuteride had an uncertain trend. The ratios of these values gave an kinetic isotope effect for each tube, the average of which was 1.66.

2.6 Electrophilicity of Distonic Radical Cations

Electrochemical Studies

In the event that distonic radical cations could be generated and then reduced electrochemically, it seemed possible that one could possibly correlate electrophilicity with reduction potentials. We therefore decided to perform electrochemical studies on these species. Medébielle and co-workers have shown that direct and indirect electrochemical reduction of perfluoroalkyl halides in aprotic solvents leads to the formation of the corresponding perfluoroalkyl radicals through a concerted one-electron transfer bond breaking mechanism (Equation 2-2).⁷²



With this in mind, our goals included: (1) generating the distonic radical cation by electrochemical means; (2) obtaining a value for the reduction potential of the radical; (3) comparing the reduction potential to those of fluorine substituted radicals; and (4) determining if there is any correlation between the electrochemical reduction potentials and the chemically observed electrophilicity.

The reduction potentials for these substrates were obtained in acetonitrile by means of microelectrode techniques, viz. cyclic voltammetry, with tetrabutylammonium hexafluorophosphate as the supporting electrolyte. Table 2-4 summarizes the results obtained from the electrochemical experiments.

Table 2-4. Peak Potentials vs. SCE for the first cyclic voltammetric reduction wave of various iodides in acetonitrile at the gc electrode using Bu₄NPF₆ as the supporting electrolyte.

Substrate	Peak Potential @ 0.25V/s
(CH ₃) ₃ N ⁺ CH ₂ I BF ₄ ⁻ , 2-1	-1.39
C ₇ F ₁₅ I, 2-46	-1.19
CF ₃ CH ₂ I, 2-47	-1.80
C ₆ F ₁₃ CH ₂ CH ₂ I, 2-48	-2.0

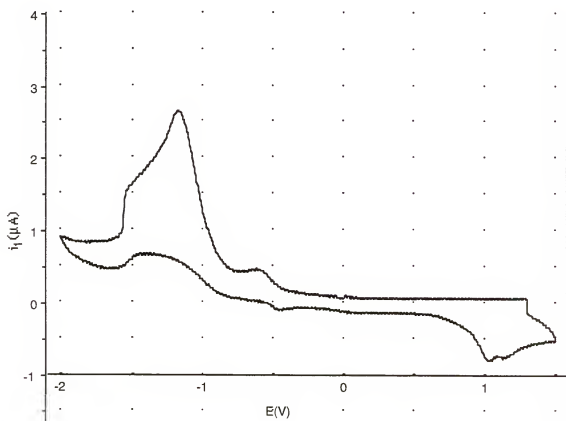


Figure 2-24. Voltammogram of **2-1** at a gc electrode vs. silver/silver chloride electrode in CH₃CN and 0.1M NBu₄BF₄ at a scan rate of 0.25V

Figure 2-24 shows the cyclic voltammogram obtained with the iodomethyltrimethylammonium tetrafluoroborate (**2-1**) on a glassy-carbon electrode in acetonitrile at a low rate scan (0.25V/s). The peak width and peak potentials showed good reproducibility. The first major wave is attributed to the irreversible single electron reduction at a potential close to -1.14V versus the Ag/AgCl electrode. This value becomes -1.39V vs. the saturated calomel electrode (SCE).

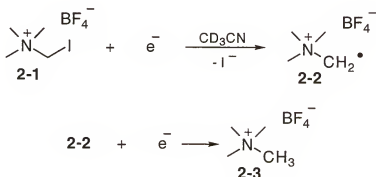


Figure 2-25. Electrochemical reduction of **2-1** to give **2-3**

The electron transfer is a dissociative process (Figure 2-25), as seen previously in our liquid phase experiments (Section 2-2). The current dip observed after the first reduction potential may be explained as an autocatalytic process triggered by a *solution* electron transfer, possibly between the reduced product, **2-3**, and the reactant. Similar voltammograms have been obtained for electrochemically induced $S_{RN}1$ reactions of perfluoroalkyl iodides.⁷³⁻⁷⁷

Figure 2-26 shows a voltammogram obtained with perfluoroheptyliodide, **2-46**. The voltammogram is typical of all the fluorinated compounds which are reduced irreversibly. More than likely, the reduction is a dissociative electron transfer process where the electron transfer and the bond-

breaking are concerted. The radical anions of the alkylhalides cannot be observed in the cyclic voltammogram experiments.

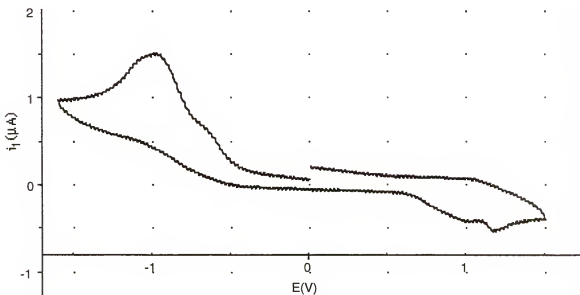


Figure 2-26. Voltammogram of $C_7F_{15}I$ (3mM) at a gc electrode vs. silver/silver chloride in CH_3CN and 0.1M NBu_4PF_6

From the data shown in Table 2-3, it is observed that for each methylene unit that is introduced, the reduction becomes more difficult as shown by the decreasing values for the reduction potentials. For instance, CF_3I has been reported to be reduced irreversibly at -1.55V vs. SCE, in acetonitrile,⁷² while CF_3CH_2I is irreversibly reduced at -1.80V vs. SCE. Another example is where $C_6F_{13}I$ is reduced at -1.29V vs. SCE⁷⁶ while $C_6F_{13}CH_2CH_2I$ is reduced at -2.00V vs. SCE.

Attempts to correlate reduction potential to electrophilicity based on chemically derived rate constants were not very rewarding. When the natural logarithm of the rate constants for 2-1, 2-46, and 2-47 were plotted as a

function of the reduction potentials, the regression was found to be less than 8, indicating little or no correlation between the two parameters.

2.7 Single Electron Transfer (SET) Reduction

The unusual result in the electrochemical study of α -ammonio distonic radical cations prompted us to investigate the possibility of these species being involved in single electron transfer (SET) reactions. We therefore chose to react our iodomethyl ammonium salt **2-1** with thiophenoxide, a nucleophile widely used in SET processes, under both thermal and photochemical conditions. Any displacement of the iodide to give **2-49** (Figure 2-27), would be considered strong evidence for an SET mechanism.

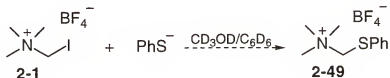


Figure 2-27. Expected reaction for an SRN1 mechanism involving **2-1** and thiophenoxide.

A 35mM solution of **2-1** in 1:1 methanol- d_4 and benzene- d_6 was irradiated in the presence of one molar equivalent of sodium thiophenoxide under an oxygen-free atmosphere for 40min. Proton NMR analysis of the reaction mixture showed that about 50% of **2-1** was converted to **2-49** during that time. When the reaction was allowed to continue for longer periods, that is, 2h or more, the reaction mixture become quite complicated showing that multiple processes were occurring. In ambient light, **2-49** was not formed.

2.8 Discussion

Alkene Additions

The observed rate constant for the the 6-exo cyclization of **2-9** (Figure 2-28) at 33°C was found to be 200 times faster than that of the analogous 6-heptenyl system while the cyclization rate of **2-13** was found to be 60 times faster than its hydrocarbon analog. The enhanced reactivities which are observed for these species derive from some combination of three factors: electrophilicity, enthalpic effects, and the *gem*-dimethyl effect. Beckwith has found that *gem*-dimethyl substituents at the 2-position lead to a ~16-fold rate enhancement for 5-exo-hexenyl cyclizations.⁶² Assuming that there are similar rate enhancements for 6-exo-heptenyl cyclizations, the net enhancements due to the ammonio substituents in the cyclizations of **2-11** and **2-13** are ~4 and ~12, respectively.

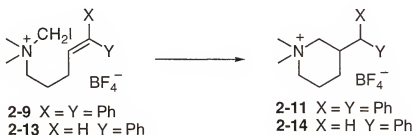


Figure 2-28. Cyclizations of **2-9** and **2-11**.

While these net enhancements are small, they are still significant. With a ρ value of only -0.23, it is certain that the ammoniomethyl radical is somewhat

Dolbier and co-workers⁷¹ performed calculations on the relative stability of distonic radical cations and their conventional isomers. Like Radom, they found that the parent distonic radical cation, $\text{H}_3\text{N}^+\text{CH}_2^\bullet$, is only slightly more stable than its conventional isomer, $\text{H}_2\text{N}^+\text{CH}_3$. In contrast, the methyl-substituted analog, **2-2**, was disfavored by more than 12kcal/mol, relative to its conventional isomer, $(\text{CH}_3)_2\text{N}^+\text{CH}_2\text{CH}_3$.

$$\begin{array}{c}
 \text{Ph} \text{---} \text{N}^+ \text{---} \text{BF}_4^- \text{---} \text{SPh} \\
 | \\
 \text{2-36}
 \end{array}
 \xrightarrow[\text{C}_6\text{D}_6/\text{CD}_3\text{OD}]{\text{nBu}_3\text{SnH}}
 \begin{array}{ccc}
 \begin{array}{c} \text{Ph} \text{---} \text{N}^+ \text{---} \text{BF}_4^- \\ | \\ \text{2-37} \end{array}
 & + \quad \text{PhCH}_2\text{OCD}_3 \quad \text{2-38} \quad + \quad \text{PhCH}_3 \quad \text{2-39} \\
 \\
 \begin{array}{c} \text{---} \text{N}^+ \text{---} \text{BF}_4^- \\ | \\ \text{H} \\ \text{2-40} \end{array}
 & + \quad \begin{array}{c} \text{---} \text{N}^+ \text{---} \\ | \\ \text{---} \end{array}
 \end{array}$$

Figure 2-29. Cleavage of benzylsubstituted ammonium salt **2-36** to give products from heterolytic and homolytic cleavage.

The unusual results that were obtained in our attempt to observe homolytic cleavage of the benzylammonium salt, **2-36** (Figure 2-29), are in agreement with numerous other systems already reported in the literature.⁸⁰⁻⁸⁷

In 1971, Kochi and Ratcliff⁸⁰ reported that various benzylammonium halides undergo concurrent heterolytic and homolytic decomposition under photolytic conditions. They found that in alcohol solutions, photolysis of these benzyl containing ammonium salts produced benzylethers and amines (Figure 2-30 (a)). They proposed that a competing homolytic process generated toluene and an aminocarbenium ion (which is isolated as the alkoxybenzyltrimethylamine) by a cage disproportionation of the benzyl radical with its aminium fragment (Figure 2-30 (b)).

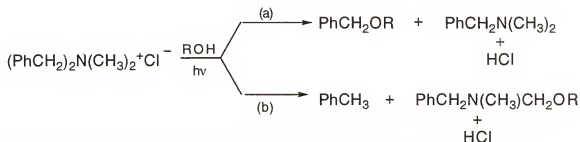


Figure 2-30. Photochemically induced heterolytic and homolytic cleavage of benzyl-substituted ammonium salts; (a) products from heterolytic cleavage, (b) products from homolytic cleavage.

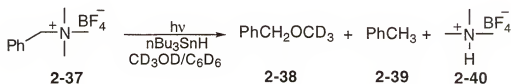


Figure 2-31 Cleavage of the trimethylbenzyl ammonium salt.

In the same paper,⁸⁰ Kochi and Radcliffe report that the benzyltrimethylammonium salt, **2-37**, undergoes photochemically induced fragmentation by both the heterolytic and homolytic mechanisms concurrently.

We observed similar results when we irradiated **2-37** in a methanol/benzene mixture (Figure 2-31). These observations explain the unusual results obtained when **2-36** is reacted under photochemical conditions with a large excess of tributyltin hydride. Both the starting material, **2-36**, and its reduced product, **2-37**, would be cleaved heterolytically and homolytically when photolysed. This was further confirmed when the reaction mixture from the reaction described in Figure 2-29 was irradiated for extended periods of time (12h). From proton NMR analysis, the reduced product (**2-37**) was observed to decrease while fragmentation products (**2-39** and **2-40**) increased.

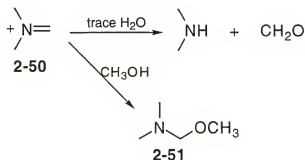


Figure 2-32. Reaction with Eschenmoser's Salt

It was also quite interesting to discover the fate of the dimethyl(methylene)ammonium species during the course of the reaction. It was expected that the iminium salt (**2-50**) would be hydrolysed to form formadehyde and dimethylamine (Figure 2-32), or react further with methanol-*d*₄ to form the alkoxy amine. Independent studies which were performed with commercially available Eschenmoser's Salt, **2-50**, showed that it reacted with

methanol to slowly form **2-51**. The results from these reactions were very different from the results obtained in our cleavage experiments.

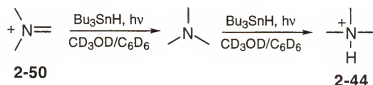


Figure 2-33. Reduction of Eschenmoser's Salt with tributyltin hydride.

Products obtained from the consumption of reactive **2-50** were identified as trimethylamine and trimethylammonium salt by mass spectral analysis of the reaction mixture (Figure 2-33). The presence of these products were further confirmed by proton NMR when authentic samples were added to the reaction mixture. These observations were again confirmed when tributyltin hydride was added to commercially available Eschenmoser's Salt, giving immediate and total conversion to trimethylamine.

Similar types of transformations have been reported in the literature.⁸⁸ Hosomi and co-workers^{88(a)} have reported that reduction of alkylthiomethylene iminium iodides by trimethoxysilane and dilithium 2,3-butandiolate, proceeds smoothly to give S, N-acetals selectively in high yield (Figure 2-34).

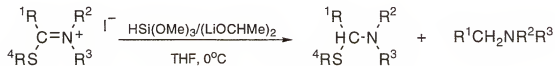


Figure 2-34. Selective reduction of alkylthiomethyleniminium salts.

The Allylic System

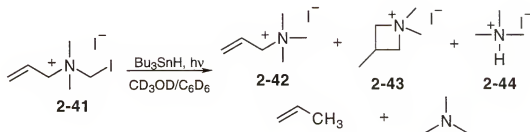


Figure 2-35. Reaction of **2-41** with tributyltin hydride.

Not surprisingly, the radical generated from the irradiation of **2-41**, readily abstracted a hydrogen atom from tributyltin hydride to give **2-42**. The directly reduced product, **2-42**, and the trimethylammonium salt **2-44** were easily identified when authentic samples of the salts were added to the reaction mixture and the peaks corresponding to **2-42** and **2-44** increased accordingly. Mass spectral analysis of the reaction mixture further confirmed that these products had formed.

Proton NMR analysis of the reaction mixture gave the first indication that the cyclized product, **2-43**, had formed. In the proton NMR spectrum, two singlets at δ 2.83 and 2.88ppm of similar intensity were observed. A doublet at δ 1.06ppm having similar integration to the two singlets was also observed. These observations were explained further when mass spectral analysis of the non-volatile components of the reaction showed only one molecular ion, 286. Since **2-42** and **2-43** are structural isomers, a single molecular ion would be expected. This result prompted us to believe that the azetidinium salt had been formed.

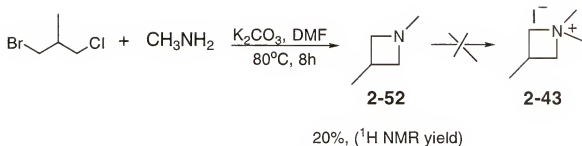


Figure 2-36. Attempt to synthesize azetidinium salt, **2-43**.

Attempts to independently synthesize **2-43** proved to be quite unsuccessful; however, this was not surprising since in general, azetidines and azetidinium salts are not readily accessible. We first tried to synthesize the salt by first making the azetidine **2-52** based on literature precedent,¹⁰⁹ and then quaternizing the nitrogen (Figure 2-36) to get **2-43**. The azetidine, **2-52**, was obtained as a crude product in DMF in 20% yield. While we were able to synthesize the azetidine in very low yield, attempts to methylate **2-52** with methyl iodide were unsuccessful.

Since synthesis of the salt **2-43** and separation of the salt mixture seemed futile, we resorted to characterizing **2-43** while in the presence of the other ammonium salts, **2-42** and **2-44**. For this purpose, we used a two dimensional NMR method to analyze the mixture of salts obtained from the reaction. The method used was Totally Correlated Spectroscopy (TOCSY), a method that is very similar to COSY (Correlated Spectroscopy). The spectra obtained from this analysis is shown in Figure 2-37(b). The ^1H NMR signals were assigned based on the homonuclear correlations seen in the TOCSY spectrum and on the integral values.

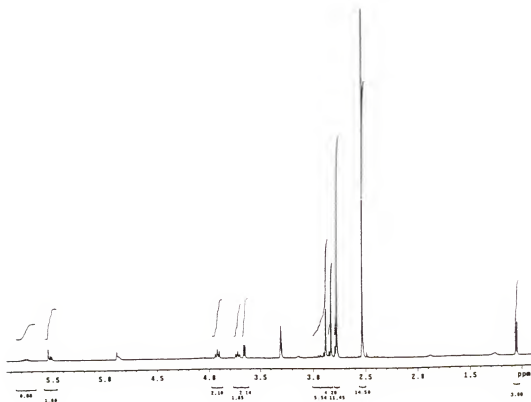
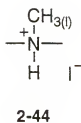
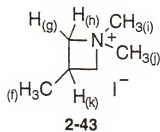
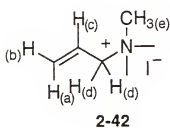


Figure 2-37. ¹H NMR spectrum obtained for the mixture of **2-42**, **2-43** and **2-44** (resonance at δ 4.9ppm for water is suppressed).

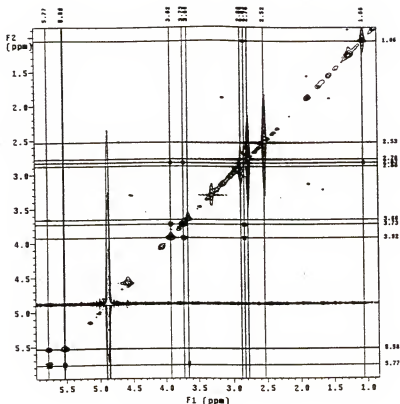


Figure 2-38. TOCSY spectrum obtained for the mixture of **2-42**, **2-43** and **2-44**.

The TOCSY spectrum is a homonuclear correlation two dimensional spectrum. It was preferred over COSY because the digital resolution could be limited to the chemical shift separation once all the peaks were in phase, and also because the experiment time is shorter.

The resonance at δ 2.53ppm (H_l) is not coupled to anything which is expected since it derives from the trimethylammonium salt, **2-44**. The signal at δ 5.77ppm was assigned to H_c of **2-42** based on its chemical shift and splitting pattern. It couples to two doublets at 5.54 and 5.53 which were assigned to H_b and H_a , respectively, based on the value of the coupling

constants. H(c) also couples to a doublet at 3.66ppm which corresponds to H(d). The integral values were consistent with these assignments and also allowed the assignment of the signal at 2.83ppm to the three methyl groups, H(e).

For the azetidinium salt **2-39**, the doublet at δ 1.06ppm was assigned to the protons, H(f) in the methyl group based on its chemical shift and multiplicity. The TOCSY spectrum revealed the coupling between H(f) and a multiplet buried under the singlet at 2.83. The multiplet was assigned to the methine proton H(k). H(f) displays cross peaks with signals at 3.92 and 3.73 which are coupled together. These two signals were assigned to the two diastereotopic protons H(g) and H(h). The integral values were consistent with these assignments and also allowed the assignment of the singlets at 2.83 and 2.78 to the two methyl groups H(l).

So far, the allyldimethylmethylene ammonio radical is the only distonic radical that has exhibited such versatility. While the reduction of the radical and the cleavage reactions were not surprising, it was quite interesting to observe 4-exo cyclization occurring so readily. It is quite likely that the facile cyclization is influenced by some of the reasons previously discussed in this section, that is, *gem*-dimethyl effect and electrophilicity.

The rapid cyclization of **2-41** may be compared that of 5-pentenylbromides to form cyclobutanes.⁹⁰ According to Jung and co-workers, *gem*-dialkoxy groups accelerated the 4-exo-pentenyl cyclization even more so than the *gem*-dimethyl groups (Figure 2-39).

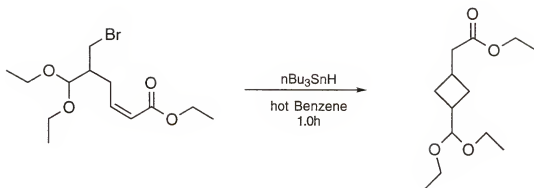


Figure 2-39. Formation of cyclobutane by rapid 4-exo-pentenyl cyclization.

Baldwin⁹¹ has developed a system whereby ease of ring closure may be correlated with the stereoelectronic requirements of the transition state. They have classified ring closure with respect to three factors: (a) ring size, (b) the hybridization of the carbon at the reaction site, and (c) the relationship (endocyclic or exocyclic) of the reacting bond to the forming ring. Based on these factors, it is now commonly accepted that in general, the relative order for ease of formation of ring systems is $5 > 6 > 3 > 7 > 4 > 8-10$.^{92,93}

The enthalpy of activation ($\Delta H^\ddagger$) for the formation of three- and four-membered rings is normally higher than $\Delta H^\ddagger$ for the corresponding five- and six-membered rings. The entropy of activation ($\Delta S^\ddagger$) however, is least negative for the three-membered rings, of comparable magnitude for four-, five- and six-membered rings, and becomes more negative as the ring size increases above seven. The strain which develops in the closure of the smaller rings is represented by the $\Delta H^\ddagger$ term while the large negative entropy associated with the larger rings shows the improbability of achieving the required molecular orientation for closure. These arguments certainly explain our surprise at the relative ease of formation of **2-43**.

Kinetic Isotope Effect

Typically, a primary isotope effect of $k_H/k_D \geq 2$ is expected for hydrogen abstraction by radicals. In these reactions, the bond to the isotopically labelled hydrogen atom is being broken in the rate-determining step. For distonic radical cations, the kinetic isotope effect is low (1.62), but still considered to be a primary isotope effect. This relatively low value implies that the rate determining step may not be what one would typically expect.

One could propose several possibilities to explain our observations. Trialkyltin hydrides have been shown to undergo acetolysis in the presence of halide ion.⁹⁴ It is suggested that the mechanism involves a pre-rate-determining coordination of the halide ion on tin. This process activates the hydride ion, allowing for facile attack by acetic acid (Figure 2-40). The stannyl anion then readily releases a hydride ion. In our system, one could propose that the neutral tributyltin hydride (or deuteride) abstracts fluoride from the tetrafluoroborate anion to become the negatively charged, pentavalent ion, **2-53** (Figure 2-41).

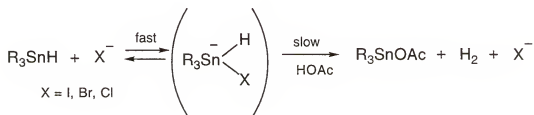


Figure 2-40. Acetolysis of trialkyltin hydride assisted by halide ion.

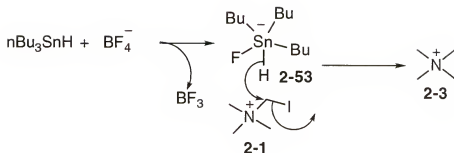


Figure 2-41. Possible mechanism for the reduction of **2-1**

Once the hydride is released, it may then displace the iodide from **2-1** to form the reduced product. This mechanism is supported by the presence of tributyltin fluoride in the reaction mixture, as indicated by ^{19}F NMR spectroscopy. Also, for such a mechanism, one would expect an inverse isotope effect since deuteride is a better nucleophile than hydride.

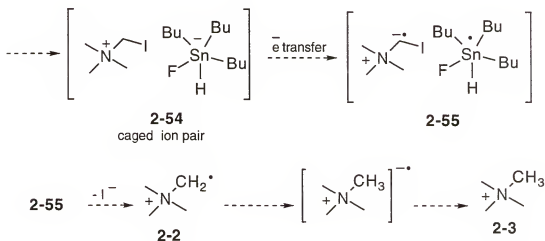


Figure 2-42. Alternative mechanism for the reduction of **2-1** involving a caged ion pair.

While the mechanism proposed in Figure 2-40 is plausible, one can also propose another mechanism involving a radical intermediate. Figure 2-42

shows a mechanism where radical **2-2** is formed by an electron transfer process and is then reduced by the hydride.

2.8 Conclusion

It is quite evident that α -ammonio distonic radical cations perform both gas phase and solution phase reactions that are typical of inert, alkyl radicals. They have been successfully generated in solution as well by electrochemical means. We have shown that these radicals readily abstract hydrogen from a number of radical reducing agents. We have also successfully demonstrated that these species undergo facile unimolecular alkene addition reactions by performing 4-exo-, 5-exo- and 6-exo cyclizations. It is therefore still puzzling that we have seen very little intermolecular reactions with olefins.

We have identified α -ammonio distonic radical cations to be very reactive species capable of performing numerous reactions. Not only do they abstract hydrogen and add to alkenes, but they also undergo photochemically induced single electron transfer reactions. In kinetic isotope effect studies, it has been shown that abstraction of the hydrogen atom is the rate determining step in the reduction of α -ammonio distonic radical cations. Still, there are numerous ambiguities which direct us to study further the peculiarities of these very unusual species.

CHAPTER 3 DEALKYLATION OF HALOMETHYLTRIALKYLAMMONIUM SALTS

3.1 Introduction

Quaternary chloro-methylated ammonium salts (Figure 3-1) have been shown to possess potent, growth inhibitory activity against the proliferation of a highly human, tumorigenic, gastric cancer cell line, HGT-1.⁹⁵ The activity has been attributed to the presence of a quaternary ammonium group which is responsible for some alkylating effect.

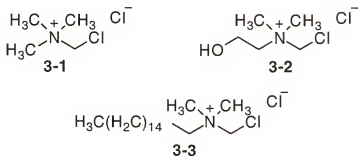


Figure 3-1. Chloromethylammonium salts active against HGT-1

A similar type of alkylating effect was described twenty-two years prior by Albert Eschenmoser as he described the synthesis of the dimethyl(methylene) ammonium iodide **3-6** (Figure 3-2), otherwise known as Eschenmoser's Salt.⁹⁶ According to Eschenmoser, methyl iodide and **3-6** were formed after fifteen minutes in better than 80% yield when iodomethyltrimethylammonium iodide, **3-4**, was heated in sulfolane at 150°C. He also observed that when tetramethylammonium iodide, **3-5**, was subjected to the same reaction

conditions, no de-methylation occurred. In fact, when **3-5** was heated up to 200°C, very little methyl iodide was formed. These experiments led Eschenmoser to propose that the demethylation of **3-4** occurred by a concerted, S_N2 mechanism, via a (n-σ, σ-π) fragmentation.

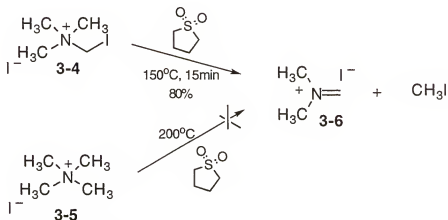


Figure 3-2. Results from Eschenmoser's De-methylation Experiments

Since that time, very little has been reported in the literature regarding Eschenmoser's hypothesis, until now. While studying the reactivity of α -ammonium distonic radical cations in solution (Chapter 2), we observed curious results that led us to re-examine fragmentation reactions previously studied by Eschenmoser. The distonic radical cations were generated preferably from their iodomethyl precursors which were synthesized by reacting the appropriate tertiary amine with diiodomethane.⁶⁸ Surprisingly, in the cases where the amine was either benzyldimethyl amine or cinnamyl dimethyl amine, the expected iodomethyl salts, **3-7** and **3-9** were not observed (Figure 3-3). Instead, the bis adducts **3-8** and **3-10** were formed in better than 80% yield. When the reaction between diiodomethane and benzyldimethylamine was repeated in the presence of methanol, the iodomethyl salt, **3-7**, was detected in the reaction mixture along with the bis adduct, **3-8**. After five days, **3-7** was

completely converted to **3-8**. This experimental result suggested that both of the bis adducts were formed by a rapid nucleophilic attack on the desired iodomethyl ammonium salts, possibly by the same mechanism proposed by Eschenmoser.⁹⁶ Since there was no evidence that a benzyl cation was trapped by methanol to give benzylmethylether, a unimolecular mechanism seemed to be unlikely. This then led to the assumption that the dealkylation for the iodo-methylammonium salts followed an S_N2-type mechanism.

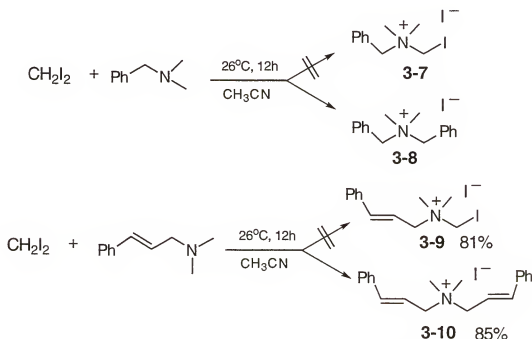


Figure 3-3. Synthesis of unexpected bis-ammonium adducts

In the event that these unusual products were formed by some type of bimolecular process, there was still the question of what was the nature of the S_N2 mechanism, that is, was the de-alkylation occurring by a stepwise process, or was it following a synchronous process as suggested by Eschenmoser. Should the de-alkylations occur by a stepwise mechanism (Figure 3-4), it can be assumed that the kinetic influence of the halogen substituent of

$(\text{CH}_3)_3\text{N}^+\text{CH}_2\text{X}$ should derive only from its influence on the leaving group ability of the amine, $(\text{CH}_3)_2\text{NCH}_2\text{X}$. In other words, its influence should depend directly and simply on the electronegativity of the halogen. In contrast, if the reaction proceeded by synchronous pathway (Figure 3-5), then the influence of the halogen substituent would depend primarily upon its leaving group ability and very little on its electronegativity. Based on this premise, we determined to investigate this interesting reaction in an effort to further elucidate the reaction mechanism.

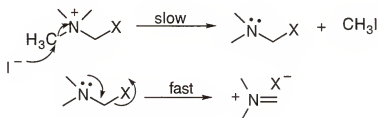


Figure 3-4. Stepwise $\text{S}_\text{N}2\text{-E}_1$ mechanism



Figure 3-5. Synchronous $\text{S}_\text{N}2$ mechanism

3.2 Trimethylhalomethyl Ammonium Salts

In order to distinguish between a stepwise and a synchronous bimolecular fragmentation mechanism, a series of halomethyltrimethylammonium salts would be reacted with one nucleophile, and the rates of de-

methylation in each system measured by reaction kinetics (Figure 3-6). If the reaction proceeded by a stepwise mechanism, it is expected that the rates of de-methylation for **3-4**, **3-11**, **3-12** would be $X = \text{Cl} > \text{Br} > \text{I}$, based on the order of electronegativities of the halogens.⁵⁰

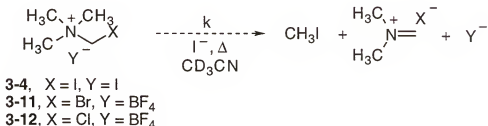


Figure 3-6. Halomethyltrimethylammonium salts used in de-methylation study

Since halogens have an inverse relationship between their leaving group abilities and their electronegativities,⁵⁰ it is expected that the opposite trend would be observed if the reaction went through a synchronous mechanism. One would also expect that for a $\text{S}_{\text{N}}2\text{-E}_1$ mechanism, if X is an oxygen-containing group such as a methoxy group, the fragmentation would occur at a rate similar to that of **3-12** since oxygen and chlorine have similar electronegativities.⁵³

Precursor Syntheses and Reaction Kinetics

All salts used in the study were easily prepared by reacting the appropriate dihalomethane with trimethylamine in acetonitrile.⁶⁸ The de-methylation reactions were performed in sealed NMR tubes, either heated in a constant temperature oil bath or in a Gemini 300MHz NMR spectrometer probe. All reactions that required temperatures less than 75°C, were heated in the Gemini 300MHz spectrometer probe. All others were heated in the constant

temperature oil bath. Regardless of the method of heating, all reactions were monitored by proton NMR spectroscopy.

Iodomethyltrimethylammonium Iodide (3-4)

Using the procedure described by Almarzoqi *et al*, **3-4** was synthesized in excellent yield when trimethylamine gas was reacted with diiodomethane in acetonitrile overnight at room temperature (Figure 3-7).⁶⁸

A 20mM stock solution of **3-4** was prepared in deuterated acetonitrile with benzene as an internal standard. It should be noted that acetonitrile-d₃ was chosen for the study because it dissolved the salts sufficiently, gave clean reactions in reasonable time, and it allowed the reaction to be monitored by proton NMR spectroscopy.⁹⁷ A 0.7ml aliquot of the stock solution was heated at 75°C and the loss of the starting material (CH₃, δ 3.3ppm) was monitored with respect to time by proton NMR spectroscopy.

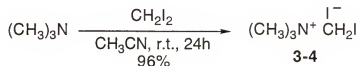


Figure 3-7. Synthesis of Iodomethyltrimethylammonium Iodide, **3-4**

A first order rate plot was made, plotting the logarithm of the relative peak decrease, which is proportional to the loss of the starting material, against time (Figure 3-8). A straight line was obtained indicating a probable pseudo-first order process⁹⁸ and the observed rate constant, k_{obs} , was obtained directly

from the negative slope of the line (Equation 3-1) and the bimolecular rate constant obtained by using Equation 3-2.

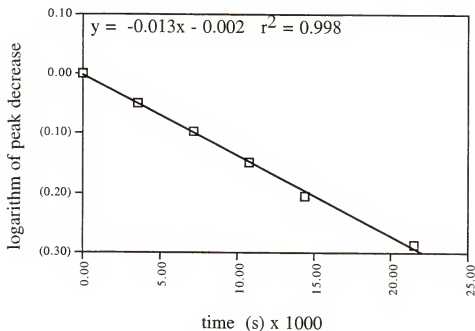
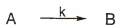


Figure 3-8. A Graph showing the natural logarithm of the disappearance of **3-4** with respect to time at 75°C. The pseudofirst order rate constant, k_{obs} , is the negative slope of the line and the bimolecular rate constant is obtained by applying Equation 3-2; r^2 is the square of the regression.



$$\text{rate} = \frac{d[A]}{dt} = k[A]$$

$$\int \frac{d[A]}{[A]} = \int k dt$$

$$\ln \left(\frac{[A]_0}{[A]_t} \right) = kt$$

$$\ln[A]_t = kt + \text{constant}$$

(3-1)

$$k_{\text{obs.}} = k_{\text{bimolec.}} [I^-] \quad (3-2)$$

Rate constants for the de-methylation of **3-4** were determined at three different temperatures so that Arrhenius parameters could be obtained. From these parameters, the rate of the de-methylation of **3-4** could be extrapolated to the higher temperatures required for analogous reactions of **3-11** and **3-12**. The results are summarized in Table 3-1. Applying this data to the Arrhenius equation (Equation 3-3), activation parameters were obtained.⁹⁹ A linear least square regression plot of $\ln(k)$ versus $1/T$ gave the energy of activation, E_a and $\log A$ from the slope and intercept, respectively. The E_a was determined to be $19.0(\pm 0.3)$ kcal M^{-1} K^{-1} with a $\log A$ of $8.7(\pm 0.2)$. The Arrhenius plot is shown in Figure 3-9.

Table 3-1 Rates for the De-methylation of **3-4**

Temperature, °C	k, $M^{-1}s^{-1}$
65	$2.8 (\pm 0.1) \times 10^{-4}$
70	$4.1 (\pm 0.2) \times 10^{-4}$
66	$6.6 (\pm 0.2) \times 10^{-4}$

$$k = A \exp\left(-\frac{E_a}{RT}\right) \quad (3-3)$$

$$\ln(k) = 2.303 \log A - \frac{E_a}{RT}$$

where:

k is the bimolecular rate constant

A is the pre-exponential factor

R is the gas constant, $1.986 \text{ cal M}^{-1} \text{ K}^{-1}$

T is the temperature in degrees Kelvin

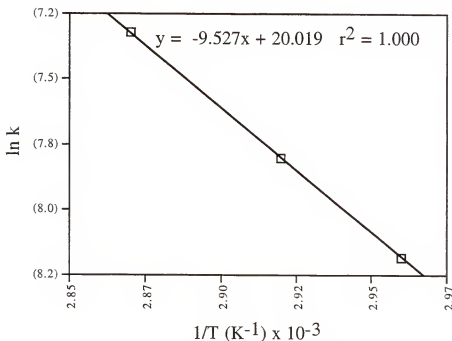


Figure 3-9. Arrhenius Plot for the De-methylation of **3-4**. Slope is -9.53 and the intercept is 20.02. $E_a = 9.53 \times 1000 R = 19 \text{ kcal mol}^{-1} \text{ K}^{-1}$ and $\log A = 20.02 / \log(e) = 8.7$

Bromomethyl- and Chloromethyl- Trimethylammonium Tetrafluoroborate

Bromomethyltrimethylammonium bromide, **3-13** and chloromethyltrimethylammonium chloride, **3-14**, were synthesized in excellent yield by reacting trimethylamine gas with dibromomethane and dichloromethane, respectively (Figure 3-10).⁶⁸ Both bromide and chloride anions were exchanged for the non-nucleophilic tetrafluoroborate anion, by reacting **3-13**

and **3-14** with silver tetrafluoroborate, in order to ensure that the counter ions did not compete with the iodide nucleophile during the kinetic studies.

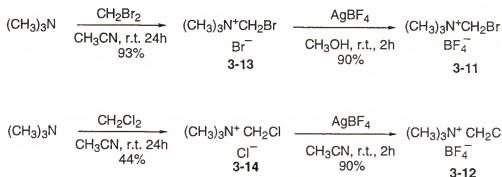


Figure 3-10. Synthesis of Bromomethyl- and Chloromethyl- Ammonium Salts

For the kinetic studies, benzyltrimethylammonium iodide was used as the iodide source due to its ideal solubility properties in acetonitrile, and its stability at the required reaction temperatures. By heating equimolar salt solutions of the bromomethyl salt with the iodide salt in acetonitrile- d_3 at 101°C , a second order rate constant was obtained as the disappearance of **3-11** was monitored by observing the decrease of its methyl peak at δ 3.22 ppm with respect to time. The rate constant for the de-methylation of **3-12** was determined in the same manner. In both cases, the methyl peak from the iodide salt, δ 3.03ppm, was used as the internal standard (Figure 3-11).

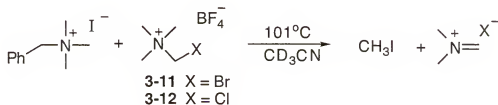


Figure 3-11. Reaction between **3-11** and **3-12** with iodide ion

The second order rate constants were determined by applying Equation 3-4^{53,97} to the data obtained from the proton NMR analyses of the kinetic reaction mixtures.



where the initial concentrations
of A and B are the same

$$\text{rate} = \frac{d[x]}{dt} = k_A(a_o - x)^2$$

$$\int \frac{dx}{(a_o - x)^2} = \int k_A dt$$

$$\frac{1}{a_o - x} = k_A t + \frac{1}{a_o} \quad (3-4)$$

Here, x is the amount of A that has reacted in a unit volume at time t , and a_o is the initial concentration of A. Thus, for second order reactions where the reactants have the same concentration at time zero, and are assumed to be consumed at the same rate during the course of the reaction, plots of the reciprocal concentration of the reactant at any time, t , versus the time in seconds give straight lines with slopes equal to the rate constant, k . The rate constants for demethylation of the bromomethyl salt, **3-11**, and chloromethyl salt, **3-12**, were found to be $1.9(\pm 0.1) \times 10^{-5} \text{ M}^{-1}\text{s}^{-1}$ and $4.8(\pm 0.1) \times 10^{-6} \text{ M}^{-1}\text{s}^{-1}$, respectively.

The absolute bimolecular rate constant for the de-methylation of **3-11** was also determined at 101°C when two molar equivalents of the iodide were used. In this case, a plot was made based on Equation 3-5,^{53,99} a variation of equation 3-4, since the initial concentrations of starting materials were unequal. The slope of the line is the product of the rate constant, k , and the initial

concentration of the nucleophile. The corresponding plot is depicted in Figure 3-12.



where the initial concentrations
of A and B are different

$$\text{rate} = \frac{d[x]}{dt} = k_A(a_o - x)(b_o - x)$$

$$\int_0^x \frac{dx}{(a_o - x)(b_o - x)} = \int_0^t k_A dt$$

$$\frac{1}{a_o - b_o} \ln \left[\frac{b_o(a_o - x)}{a_o(b_o - x)} \right] \Bigg|_0^x = k_A t$$

Since $2a_o = b_o$, and $a = a_o - x$

$$- \frac{1}{a_o} \ln \left[\frac{2a}{a_o + a} \right] = k_A t$$

$$\ln \left[\frac{a_o + a}{2a} \right] = a_o k_A t$$

$$\ln \left[1 + \frac{a_o}{a} \right] = a_o k_A t + \ln 2 \quad (3-5)$$

The variables for Equation 3-5 are the same as in Equation 4 except for b_o , which is the initial concentration of reactant B, and b , which is the concentration of B at any time, t .

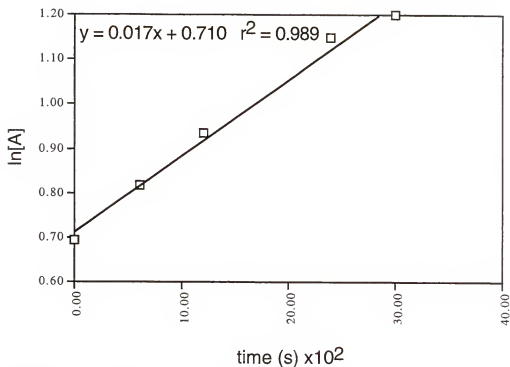


Figure 3-12. A Graph showing the results of reacting **3-11** with two equivalents of iodide. The slope is a_0k where a_0 is the initial concentration of the iodide.

The second order rate constant where two equivalents of iodide was used, was determined to be $1.7(\pm 0.1) \times 10^{-5} \text{M}^{-1} \text{s}^{-1}$

The Methoxymethyl System

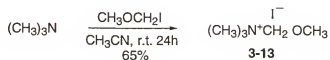


Figure 3-13. Synthesis of methoxymethylammonium precursor

By reacting three equivalents of commercially available iodomethylmethyl ether with trimethylamine at room temperature for 24h, **3-13** was obtained in 65% yield (Figure 3-13).

When a 37mM solution of **3-13** in deuterated acetonitrile at 70°C for 50h, no reaction was observed by 300MHz proton NMR spectroscopy. In another experiment, when a 23mM solution of the same salt was heated at 130°C for 1h, no signs of the expected fragmentation were detected: however, a sharp singlet at δ 2.75ppm and a rounded peak at δ 9.6ppm were detected along with starting material. When kinetic experiments were performed to measure the rate by which **3-13** was consumed, no rate constants could be obtained since the reaction was not well-behaved.

3.3 Ethyl Substituted Halomethylammonium Salts



3-15a-c

a R = R' = R'' = CH₂CH₃

b R = R' = CH₂CH₃ R'' = CH₃

c R = CH₃ R' = R'' = CH₂CH₃

Figure 3-14. Ethyl substituted salts used in relative rate study

In an effort to further investigate the dealkylating effect of iodide on trialkylammonium salts, we turned our attention to salts with differing alkyl

groups within the same molecule. The goals of this study were to get absolute rate constants for the dealkylation of the substrate, compare these rate constants to each other and to that of the trimethyl analog, and observe the relative rates of formation for the different alkyl iodides that would be formed in each system. For this study, ethyl substituted salts **3.15a-c** were chosen (Figure 3-14).

All three salts were synthesized by reacting the appropriate tertiary amine with diiodomethane, according to the methodology used to synthesize the trimethyliodomethyl analog, **3-4**.⁶⁸ Unlike the trimethyl systems however, the ethyl substituted salts were synthesized in low to moderate yields. For these salts, all kinetic reactions were performed in sealed tubes and heated in a constant temperature oil bath at 101°C. Absolute rate constants were determined for all three systems by following the loss of starting material with respect to time, and by plotting the logarithm of the peak decrease against time. Bimolecular rate constants were derived by applying Equation 3-2 to the observed, unimolecular rate constants which were obtained directly from the slopes of the lines.

Synthesis and Reactivity of Triethyliodomethyl Ammonium Iodide **3-15a**

When one equivalent of diiodomethane was reacted with three equivalents of triethylamine at room temperature for 48h, only 47.7% of iodomethyltriethylammonium iodide (**3-15a**) was obtained after purification. The low yield should most likely be attributed to the fact that the bulky triethylamine is less nucleophilic than trimethylamine. According to Almarzoqi,⁶⁸ 81% of the mono adduct is obtained when two equivalents of triethylamine is reacted with an equivalent of dibromomethane at 30°C and 5kbar after 144h. In our case, no further attempt was made to optimize the yield

of **3-15a**. It is expected though that a longer reaction time, or an increase in pressure would have caused **3-15a** to be produced in a higher yield.

Kinetic studies were conducted on 20mM stock solution of **3-15a** in deuterated acetonitrile with benzene as an internal standard, at 101°C. The conversion of **3-15a**, to produce ethyl iodide and diethylmethylene ammonium iodide, was monitored by observing the disappearance of the methylene peak (CH_2I , δ 5.1ppm) with respect to time. As in the case of the trimethyl system, the pseudo first order rate constant was obtained as the negative slope of the plot of the natural logarithm of the decrease of the starting material against time in seconds. The rate constant was observed to be $5.7(\pm 0.1) \times 10^{-5} \text{s}^{-1}$ and by applying equation 3-3, the bimolecular rate constant was determined to be $2.79 (\pm 0.05) \times 10^{-3} \text{M}^{-1} \text{s}^{-1}$. As a result, the trimethyl analog, **3-4**, was found to be 1.6 times faster than **3-15a**, which had a de-alkylation rate constant of $4.3 \times 10^{-3} \text{M}^{-1} \text{s}^{-1}$ at 101°C.

Synthesis and Reactivity of Diethylmethyliodomethyl Ammonium Iodide **3-15b**

Only 9.2% of the desired iodomethyl salt, **3-15b**, was obtained when diiodomethane was reacted with a seven-fold excess of diethylmethylamine at room temperature for 42h. No further attempts were made to optimize the reaction conditions to improve the yield of the product.

Kinetic studies were performed using a 21mM stock solution of the salt in acetonitrile. Again, the consumption of the starting material was monitored by following the decrease of the methylene peak at δ 4.9ppm with respect to time. The unimolecular rate constant was observed to be $1.32(\pm 0.06) \times 10^{-4} \text{M}^{-1} \text{s}^{-1}$ for the de-alkylation of **3-15b**, while the bimolecular rate constant was determined to be $6.3(\pm 0.3) \times 10^{-3} \text{M}^{-1} \text{s}^{-1}$. Thus, **3-15b** was dealkylated almost 1.5 times faster than the trimethyl analog.

Both methyl iodide (δ 2.2ppm) and ethyl iodide (δ 1.8 and 3.3ppm) were formed in this reaction. The relative rates of formation for both alkyl iodides were measured during the course of the reaction, but it was only after 2h of reaction, that a regular trend was observed. By averaging the ratios of the relative amounts of methyl iodide and ethyl iodide every thirty minutes for one and a half hours, it was found that *methyl iodide was formed 2.7 times faster than ethyl iodide.*

Synthesis and Reactivity of Ethyldimethyliodomethyl Ammonium Iodide **3-15c**

Only 47.7% of **3-15c** was obtained when one equivalent of diiodomethane was reacted with an excess of ethyldimethylamine. Again, no attempts were made to optimize the yield of the reaction.

When a 21mM solution of **3-15c** in deuterated acetonitrile was heated at 101°C, the observed rate constant was found to be $2.63(\pm 0.07) \times 10^{-4} \text{s}^{-1}$ and the bimolecular rate constant was then determined to be $1.26(\pm 0.04) \times 10^{-2} \text{M}^{-1} \text{s}^{-1}$. This rate was almost three times faster than that of the trimethyl analog, **3-4**.

The relative rate of formation of methyl iodide and ethyl iodide was determined for this system as well. During the course of the reaction, the amounts of methyl iodide and ethyl iodide were monitored by observing their corresponding peak growths at δ 2.2ppm (methyl iodide) and δ 1.8 and 3.3ppm (ethyl iodide) for thirty minute intervals, in the proton NMR spectra. Here again, the peak integrations for the first two hours gave no regular trend, but an average of the latter data points showed that methyl iodide formed 13.8 times faster than ethyl iodide, that is, methyl was the preferred nucleofuge almost 14 times over ethyl.

3.4 Allyl Substituted Halomethylammonium Salt

Our investigations of the dealkylation of various trialkyl-substituted ammonium salts continued as we turned our attention to the allyldimethyliodomethyl ammonium iodide salt, **2-37**. In chapter two, **2-37** was shown to undergo numerous transformations when a radical intermediate was generated. In this study, **2-37** is also shown to undergo a nucleophilic displacement de-alkylation reaction when it is heated in the presence of iodide ion.

Synthesis and Reactivity of the Precursor.

The salt **2-37** was synthesized by a two step process in low to moderate yield (Figure 3-15). The dimethylallylamine was first synthesized by performing a bimolecular displacement reaction on commercially available allyl bromide with a large excess of dimethylamine gas in the presence of sodium hydroxide. The allyldimethylamine was then engaged in subsequent S_N2 reaction with diiodomethane to give the desired iodomethyl salt, **2-37**.

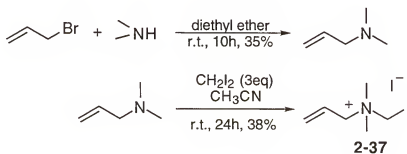


Figure 3-15. Synthesis of Allyldimethyliodomethylammonium Iodide

Unlike iodomethyltrimethylammonium iodide, the allyl-substituted salt was very soluble in acetonitrile, even at room temperature. As a result, absolute

rate constants could be obtained for the de-alkylation at very diverse temperatures. As with the aforementioned trialkyl ammonio systems, kinetic studies were conducted in deuterated acetonitrile with benzene as an internal standard; however, absolute rate constants were determined at 40°C, 50°C and 70°C. In this case, the concentration of the stock solution was 25mM. Table 3-2 summarizes the results from the kinetic reactions.

Table 3-2. Rate constants for the de-allylation of **2-37**

Temp, °C	$k_{\text{obs}}, \text{s}^{-1}$	$k, \text{M}^{-1}\text{s}^{-1}$
40	$1.2 (\pm 0.1) \times 10^{-5}$	$4.6 (\pm 0.3) \times 10^{-4}$
50	$4.6 (\pm 0.3) \times 10^{-5}$	$1.9 (\pm 0.1) \times 10^{-3}$
70	$3.9 (\pm 0.2) \times 10^{-4}$	$1.6 (\pm 0.3) \times 10^{-2}$

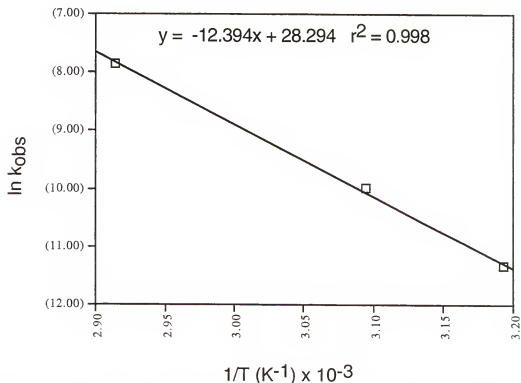


Figure 3-16. Arrhenius Plot for De-allylation of **2-37**. The slope is -12.39 and the intercept is 28.29. $E_a = 12.39 \times 1000R = 24.9 \text{ kcal M}^{-1} \text{ mol}^{-1}$ and $\log A = 28.29 / \log(e) = 12.5$

From these rate constants, activation parameters were obtained by applying Equation 3-3 and making a plot of the natural logarithm of the observed rate constants against the reciprocal of the temperatures in degrees Kelvin (Figure 3-16). Again, excellent correlation was observed as shown by the value of r^2 , the square of the regression. The energy of activation for the de-allylation of **2-37** was determined to be $24.9(\pm 1.2)\text{kcalM}^{-1}\text{mol}^{-1}$ and the $\log A$ was found to be 12.5. Using Equation 3-6, entropy of activation was determined to be -3.6cal/mol .

The bimolecular rate constants for the de-allylation of **2-37** varied with the concentration of the nucleophile. This was observed when additional kinetic studies were performed at 70°C with 2.4 and 3 equivalents of benzyltrimethylammonium iodide. As shown in Table 3-3, the unimolecular rate constants remained constant in all three studies while the bimolecular rate constants changed accordingly.

$$\Delta S^\ddagger = 4.576 \log \left(\frac{A}{T} \right) - 49.21 \quad (3-5)$$

where T is the average
temperature

Table 3-3. Change in absolute rate constants for the de-allylation of **2-37** with change in concentration of iodide at 70 °C

Equivalents of I ⁻	k (s ⁻¹)	k (M ⁻¹ s ⁻¹)
1	3.91(±0.06)×10 ⁻⁴	1.6(±0.3)×10 ⁻²
2.4	3.52(±0.02)×10 ⁻⁴	6.44(±0.01)×10 ⁻³
3	3.70(±0.07)×10 ⁻⁴	5.00(±0.10)×10 ⁻³

It should be noted that no apparent demethylation occurred during the course of the reaction.

3.4 Discussion

Halomethyltrimethylammonium Salts

In numerous studies on nucleophilic substitution reactions, it has been clearly demonstrated that the nature of the leaving group influences the rate of substitution.^{50(a)} In one such study, the relative rates of solvolysis of halides in aqueous ethanol at 75°C were determined. It was shown that the order of reactivity of the halide leaving groups is I⁻ > Br⁻ > Cl⁻ >> F⁻,¹⁰⁰ with relative rates of 91 : 14 : 1.0 : 9×10⁻⁶, an order which parallels the electron-attracting ability of the halides. This order of reactivity is opposite to that of the electronegativity of these halides and is dominated by the basicity, which ranges from ~50kcal for the C-I bond, to ~100kcal for the C-F bond.

From Table 3-4, the relative rates for the de-methylation of the halomethyl-trimethylammonium salts follow the same order of reactivity for the leaving group ability of halides. That is, the iodomethyl ammonium salt (**3-4**) is almost 900 times faster than the chloromethyl analog (**3-12**) while the

bromomethyl analog (**3-11**) is only 40 times faster. The rates of reactions for these halomethyltrimethyl ammonium salts increase according to the ability of the leaving group.

Table 3-4. Rates of the Reactions of Iodide Ion with 1-Iodo-, 1-Bromo- and 1-Chloro-N,N,N-trimethyl-methanaminium Tetrafluoroborates, **3-4**, **3-11** and **3-12**, at 101°C

X	Compound	k, M ⁻¹ s ⁻¹	k _{rel}
Cl	3-12	4.8(±0.1)×10 ⁻⁶	1
Br	3-11	1.9(±0.1)×10 ⁻⁵	40
I	3-4	4.3×10 ⁻³ (a)	896

(a)rate extrapolated to 101°C using the data in Table 3-1

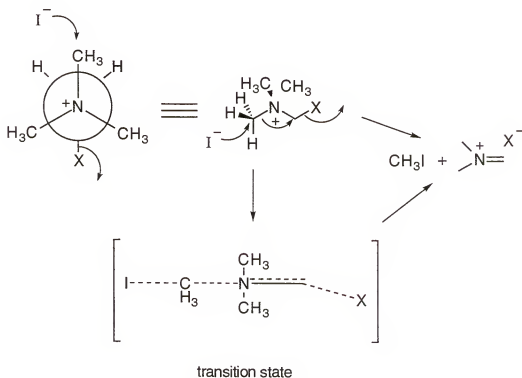


Figure 3-17. Mechanism for the de-methylation of halomethyl-trimethyl ammonium salts via a concerted, bimolecular pathway

Based on these observations, we conclude that de-methylation of halomethyltrimethylammonium salts occur by a synchronous, Grob-like fragmentation mechanism.¹⁰¹ The mechanism for the de-methylation of the trimethyl salts is depicted in Figure 3-17 while the two known mechanisms for the Grob Fragmentation are shown in Figure 3-18. It should be noted that in the Grob fragmentation, the lone pair of electrons on the nitrogen is the "nucleophile" that induces the subsequent fragmentation in the synchronous, one-step process. The two step mechanism has only been demonstrated in highly substituted systems and the results of that pathway includes numerous possible reactions, one of which is fragmentation.

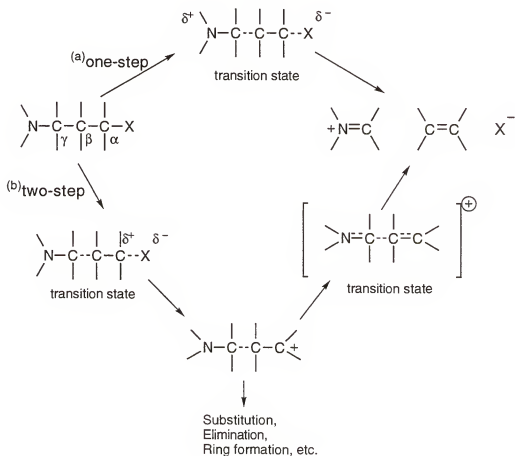


Figure 3-18. Two mechanisms for Grob Fragmentation; (a) one-step, concerted process, (b) two-step process

While the methoxy-substituted salt did not give good kinetic data that would help with the interpretation of the mechanism for de-methylation, it still gave quite interesting results. The sharp singlet around 2.8ppm was attributed to the presence of **3-5** and the rounded peak at 9.6ppm to the formation of formaldehyde. Figure 3-19 shows a mechanism that is possibly responsible for the formation of these observed products.

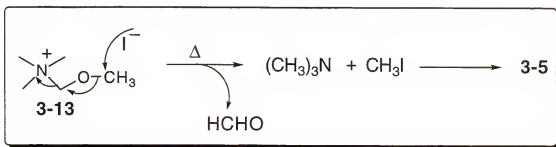


Figure 3-19. Possible mechanism for decomposition of **3-13**

Ethyl Substituted Systems

The absolute rates for the de-alkylation of ethyl-substituted iodomethylammonium salts, **3-15a-c**, and iodo-methyltrimethyl ammonium iodide, **3-4**, at 101°C are summarized in Table 3-5. Not surprisingly, when the rates of de-alkylation for the three ethyl-substituted salts are compared, it is observed that the triethyl analog, **3-15a**, is de-alkylated the slowest. For each ethyl that is replaced by methyl, **3-15b** and **3-15c**, the rate is almost doubled.

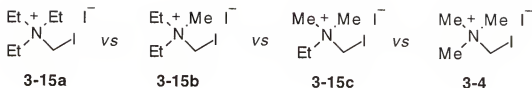


Figure 3-20. Ethyl-substituted and trimethyl-substituted salts

Table 3-5. Comparison of rate constants for the de-alkylation at 101°C of ethyl-substituted ammonium salts, **3-15a-c**, and trimethylammonium salt, **3-4**

Ammonium Salt	k ($\text{M}^{-1}\text{s}^{-1}$)
3-15a	$2.79 (\pm 0.05) \times 10^{-3}$
3-15b	$6.3 (\pm 0.3) \times 10^{-3}$
3-15c	$1.26 (\pm 0.04) \times 10^{-2}$
3-4	$4.3 \times 10^{-3} \text{ }^{(a)}$

^(a)rate extrapolated to 101°C using data in Table3-1

These observations may be rationalized when taking into account the competing de-alkylations that occur in **3-15b** and **3-15c**. For these two systems, the methyl iodide and ethyl iodide are formed in both reactions, the amounts of which indicate the relative nucleofugacity of methyl to ethyl in quaternary ammonium salts. In Figure 3-21, the trends for the growth of both methyl and ethyl iodides, during the de-alkylation of **3-15b**, are shown.

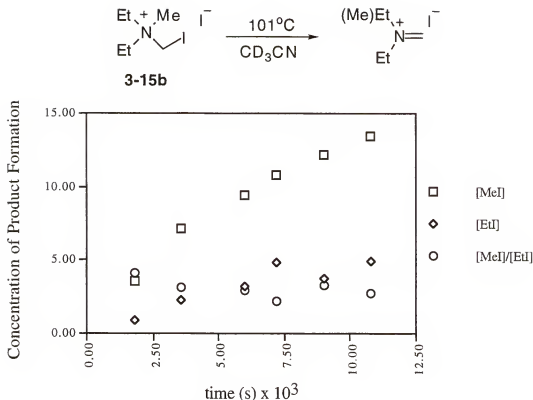


Figure 3-21 Graph showing the trend for the formation of methyl iodide and ethyl iodide during the de-alkylation of **3-15b**.

Clearly, the methyl substituent is removed at a faster rate than the ethyl group. By looking at the ratio of the concentration of methyl iodide to that of ethyl iodide over the course of the reaction, methyl iodide is formed 2.7 times faster than ethyl iodide. In fact, since there are two ethyl groups present in the molecule, the relative rate of demethylation to de-ethylation becomes 5.4:1.

In Figure 3-22, the relative rates of methyl iodide and ethyl iodide formation are shown for the de-alkylation of **3-15c**. Here, methyl iodide is formed 13.8 times faster than ethyl iodide. When consideration is made for the presence of two methyls, the relative rate of de-methylation to de-ethylation becomes approximately 7:1.

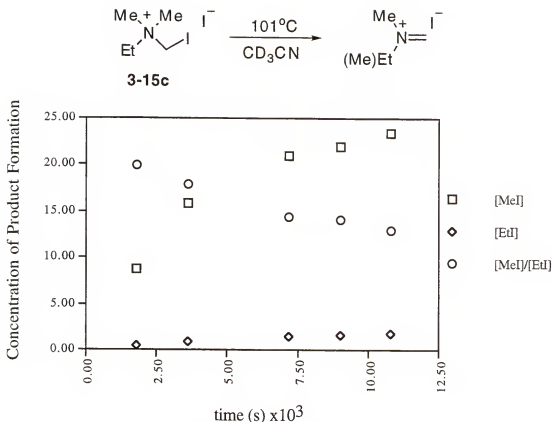


Figure 3-22. Graph showing the trend for the formation of methyl iodide and ethyl iodide during the de-alkylation of **3-15c**

By averaging the two relative rates for de-methylation and de-ethylation in **3-15b** and **3-15c**, it can be said that methyl is 6.25 times a better nucleofuge than ethyl when trialkylammonium salts are reacted with the iodide nucleophile.

Table 3-6. Statistically corrected rates for de-methylation and de-ethylation of triethyl- (**3-15a**), diethylmethyl- (**3-15b**), dimethylethyl- (**3-15c**) and trimethylammonium salts (**3-4**).

Salt	k (M ⁻¹ s ⁻¹)	[MeI]/[EtI]	k/Me (M ⁻¹ s ⁻¹)	k/Et (M ⁻¹ s ⁻¹)
3-15a	2.79 x 10 ⁻³	--	--	0.930 x 10 ⁻³
3-15b	6.3 x 10 ⁻³	2.7	4.60 x 10 ⁻³	0.851 x 10 ⁻³
3-15c	1.26 x 10 ⁻²	14	5.87 x 10 ⁻³	0.851 x 10 ⁻³
3-4	4.3 x 10 ⁻³	--	1.43 x 10 ⁻³	--

Partial rate constants for de-methylation and de-ethylation were also determined from the rate constants for **3-15a-c** and for **3-4** and the relative rates of de-methylation and de-ethylation. These results are summarized in Table 3-6. From the data it is clear that the rate at which iodide abstracts a methyl group changes in each of the ammonium salts while the rate of ethyl abstraction remains essentially the same.

A comparison between the rates of de-alkylation of the triethyl and trimethyl ammonium salts (**3-15a** and **3-4**) shows a very different ratio from the former cases where de-methylation and de-ethylation occurs within the same molecular framework. When these rates for **3-15a** and **3-4** are compared, de-methylation is only 1.5 times faster than de-ethylation. This small difference can be attributed to the fact that formation of diethyl(methylene)ammonium iodide will alleviate steric congestion in the trialkyl ammonium salt, and hence enhance to rate of de-ethylation. The positive contribution to rate of reaction counteracts some of the retarding effects which arise from ethyl being a poorer nucleofuge than methyl.

The aforementioned results are consistent with general observations made in earlier studies on bimolecular displacement reactions of nucleophiles on alkyl halides.¹⁰²⁻¹⁰⁶ In a study on the reactions of lithium bromide on alkyl iodides in acetone at 25°C, Fowden, Hughes and Ingold reported that methyl is displaced 18 times faster than ethyl.¹⁰² Conant and Hussey reported that iodide displaces methyl 93 times faster than ethyl when iodide is reacted with alkyl chlorides at 60°C in acetone.¹⁰³ In studies where the action of iodide on alkyl iodides were observed,¹⁰⁴ no comparison between the de-alkylation of methyl iodide and ethyl iodide were made. However, Streitweiser compiled the

results from numerous studies like the ones mentioned and reported that methyl is thirty times a better nucleofuge than ethyl.^{50(a)}

The Allyl-substituted System

Unlike the ethyl substituted systems, no competition between de-allylation and de-methylation was observed when iodide was reacted with **2-37**. The energy of activation for the de-methylation of the trimethyl systems was 19kcalmol^{-1} , while that for the de-allylation was 25kcalmol^{-1} . More interestingly however, the $\log A$ for the de-methylation was approximately 9, a value completely appropriate for a bimolecular process, while the $\log A$ for the de-allylation was 12. Such a large value for the pre-exponential factor aroused suspicion that the de-allylation of **2-37** was not occurring by the same bimolecular mechanism.¹⁰⁷

More insight into the mechanism for the de-allylation of **2-37** was obtained when several kinetic experiments were performed at 70°C . The rate constants were obtained for varying concentrations of the nucleophile. It is clear from the results shown in Table 3-4 that the bimolecular rate constant changes while the unimolecular rate constant stays essentially constant with change in the concentration of the nucleophile. Since the rate of reaction is obviously independent of the concentration of the nucleophile, it can be concluded that de-allylation does not occur by a bimolecular process, but by a mechanism where *the ionization step is rate determining*, most likely by an $\text{S}_{\text{N}}1$ pathway. The large pre-exponential factor, which is an indication of less ordered transition state, supports an $\text{S}_{\text{N}}1$ mechanism.

Dibenzyl and Biscinnamyl Adducts

The mechanism by which **3-8** and **3-10** are formed still remains questionable. Since the iodomethyl salts, **3-7** and **3-9** could not be isolated and subsequently studied, no definite conclusions pertaining to the mechanism for formation of the bis adducts can be made. Nevertheless, certain conjectures can be made. It is well known that a benzyl cation has stability similar to that of an allyl cation.¹⁰⁸ A cinnamyl cation would be even more stable than an allyl cation due to the extended resonance stabilization throughout the π electron framework. On this basis alone, it is very likely that bis adducts **3-8** and **3-10** were formed by an unimolecular mechanism, where stabilized cations were formed and subsequently trapped by either iodide or the tertiary amine. In the event the cations were trapped by the iodide, the newly formed alkyl iodide would undergo bimolecular displacement with the tertiary amine acting as the nucleophile.

3.5 Conclusion

It has been demonstrated that halomethyltrialkyl ammonium salts are readily dealkylated by iodide ion. The mechanism for the de-alkylation is dependent on the alkyl substituent. For systems where the alkyl group does not stabilize a positive charge readily, the mechanism for de-alkylation is via a synchronous S_N2 mechanism, a fragmentation closely resembling the synchronous, Grob Fragmentation. In this study, it was shown that the methyl group is de-alkylated approximately 6.5 times faster than ethyl group. When the ammonium salt bears a group that will readily stabilize a carbocation, that group will most likely be displaced by a mechanism that involves ionization as the rate-determining step.

CHAPTER 4 SUMMARY

The initial intent of this research project was to explore the reactivity of α -ammonio distonic radical cations. For our purposes, these species are generated from halomethyltrialkylammonium salts. While synthesizing these ammonium precursors and performing various reactions with the resulting radical intermediates, we discovered numerous surprises, all of which are quite interesting as they encouraged us to re-visit founding, physical organic theories, and discover intricate detail that had been previously ignored. Essentially, we have found that both radical and nucleophilic substitution reactions may be initiated from halomethyltrialkylammonium salts. This chapter summarizes the key observations made throughout this dissertation, and provides conclusions based on these results.

4.1 α -Ammonio Distonic Radical Cations

When iodomethyl-alkyl-dimethylammonium salts are irradiated in the presence of a radical reducing agent, the corresponding α -ammonio distonic radicals are produced. These radicals readily abstract hydrogen atom from stannyl hydride and other radical reducing agents, including *tris*(trimethylsilyl)silane (Figure 4-1). Examples of such radicals include the trimethylmethyleneammonium radical, which is discussed extensively in chapter 2.

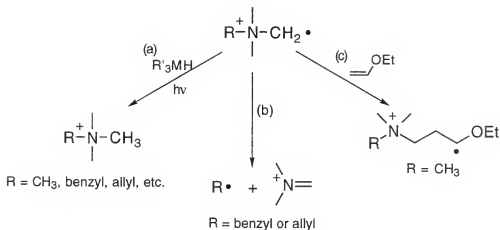


Figure 4-1. Summary of reactions of trialkylammonio distonic radical cations; (a) hydrogen abstraction, (b) cleavage, (c) intermolecular alkene addition.

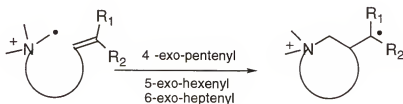


Figure 4-2. Intramolecular alkene addition of alkenyl substituted α -ammonium distonic radical cations.

α -Ammonio distonic radicals readily perform intramolecular alkene addition reactions in solution (Figure 4-2). Numerous examples of 5-exo-hexenyl cyclizations have been presented. In these examples, there has been no evidence of competition with bimolecular hydrogen abstraction reactions. Other cyclizations observed include 6-exo-heptenyl cyclizations and a 4-exo-pentenyl cyclization. In the cyclizations of the 6-exo-heptenyl systems, phenyl-substitution on the double bond enhances the rates of cyclization per phenyl substituent. The 4-exo cyclization appears to be a reversible process under

thermal conditions and is actually the preferred product when the preceeding distonic radical is generated in the presence of *tris*(trimethylsilyl)silane.

While these distonic radical cations readily abstract hydrogen atoms and perform unimolecular alkene additions, they are very reluctant to add to alkenes in a bimolecular fashion (Figure 4-1). This is uncharacteristic of radicals in general since there are numerous examples in the literature where radical-containing species have reacted with various types of olefins. The reasons for this behavior is still puzzling to us and consequently, we are in the process of trying to determine reasons for this peculiarity.

Cleavage reactions may occur in dimethyl-alkyl-methylene ammonium radicals, depending on the alkyl substituent (Figure 4-1). When the substituent is a benzylic group, both heterolytic and homolytic cleavages occur under photochemical conditions. In the presence of tributyltin hydride, these cleavages compete with hydrogen atom abstraction. The directly reduced product, trimethylbenzylammonium cation, is also cleaved by competing homolytic and heterolytic processes. The heterolytic cleavage is indicated by the trapping of the benzyl cation with the polar solvent. Only homolytic cleavage occurs by an inefficient chain process under thermal conditions.

Of all the systems studied, the allylic substituted ammonium distonic radical was the only case where three processes were observed to compete. The radical performs hydrogen abstraction, unimolecular fragmentation, and intramolecular alkene addition concurrently. It has been determined that *tris*(trimethylsilyl)silane is the best radical reducing agent for the competition study. Therefore, it is necessary to obtain a rate for hydrogen abstraction of α -ammonio distonic radical cation from this radical reducing agent.

The average kinetic isotope effect for the reduction of distonic radical cations has been found to be 1.6. This value indicates that for this reaction,

hydrogen abstraction is the rate-determining step, as is expected. Although the value is low, it is too large for a secondary isotope effect and therefore indicates a primary isotope effect.

α -Ammonio distonic radicals are electrophilic radicals. They are more electrophilic than inert alkyl radicals, but not as electrophilic as perfluoroalkyl radicals. Hammett studies on the 6-exo-heptenyl cyclizations indicate that there is delocalization to an electron-deficient site in the transition state. The transition state for the cyclization is therefore early with significant polarization.

Preliminary results show that these species perform photochemically-induced single electron transfer reaction. A specific example is the reaction between the trimethyliodomethylammonium tetrafluoroborate with thiophenoxide ion to give the trimethylthiophenoxymethylammonium salt.

Overall, α -ammonio distonic radical cations have been found to behave as inert alkyl radicals in solution. With the exception of intermolecular alkene addition, the reactivity in solution is very similar to that in the gas phase. Although this study has served to provide more information about the reactivity of distonic radical cations, there are many more questions that remain to be answered. Some of these include: (1) finding suitable conditions for intermolecular alkene additions; and (2) the possibility of (1,5- and 1,6-) intramolecular hydrogen abstraction. It is hoped that further study into the reactivity of these species would find vast mechanistic and synthetic applications. Ultimately, it is expected that the continued study of these species will find biological applications.

4.2 Dealkylation of Halomethyltrialkyl Ammonium Salts

Halomethyltrialkylammonium salts may be de-alkylated by iodide ion by one of two mechanisms. When the alkyl groups are either ethyl or methyl, the dealkylation occurs by a concerted, Grob-like Fragmentation mechanism (Figure 4-3). The evidence for the concerted mechanism was obtained during the study of the halomethyltrimethylammonium systems. The decreasing order of activity for these salts was found to be $R-I > R-Br > R-Cl$.

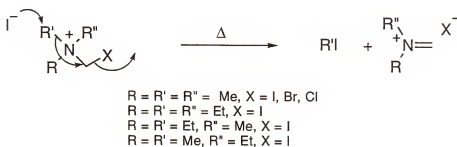


Figure 4-3. Concerted mechanism for the nucleophilic dealkylation reactions of iodide on halomethyltrialkyl-ammonium salts.

Competing de-methylation and de-ethylation occurs in ammonium salts that contain both methyl and ethyl groups within the same framework. In all cases studied, de-methylation occurs faster than de-ethylation. De-methylation was still faster than de-ethylation when independent systems (i.e. trimethyl vs. triethyl) were compared. The rate of de-methylation remains essentially constant in all systems while the relative rates of de-methylation to de-ethylation differs in the various systems.

When the rates for the three ethyl-substituted salts were compared, the triethyl-substituted ammonium salt was de-alkylated the slowest while the monoethyl-substituted salt was de-alkylated most readily. The rate of de-

methylation for the trimethylammonium system was only 1.5 times faster than the rate of de-ethylation of the triethyl system.

The allyldimethyliodomethylammonium salt is de-alkylated by a different mechanism than the simpler trialkylhalo-methylammonium salts. In this system, there is no competition between de-allylation and de-methylation. The de-allylation occurs by a unimolecular fragmentation, probably an S_N1 mechanism (Figure 4-4). This is supported by kinetic results that showed the de-allylation was independent of the concentration of the nucleophile, and a large pre-exponential factor indicating that the reaction was entropically favored.

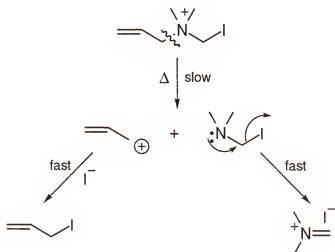


Figure 4-4. Possible mechanism for the de-allylation of the allyldimethyliodomethylammonium salt.

The mechanism for the de-alkylations of benzyl- and cinnamyl-substituted has yet to be determined. Although preliminary results suggested that the fragmentation did not occur by a unimolecular process, there is no evidence to absolutely rule out this mechanism.

CHAPTER 5 EXPERIMENTAL

5.1 General Procedures

Experimental text which mentions "commercially" available reagents indicates that such materials were purchased from Aldrich Chemical Co., Acros Organics, Fisher Scientific or Cambridge Isotopes Laboratories. All reagents were used without further purification unless otherwise indicated in the text. Solvents were dried by distilling them from the appropriate drying agent and used immediately.

Melting points were determined on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Nuclear Magnetic Resonance (NMR) chemical shifts are reported in ppm downfield from internal tetramethylsilane (TMS) for ^1H and ^{13}C NMR spectra. All spectra were obtained on Varian VXR-300 or Gem-300, and Unity-500 spectrometers. Kinetic ^1H NMR measurements were performed at 300 MHz using a Varian Gem-300 spectrometer. Mass spectra were obtained on a Finnigan MAT95Q (Finnigan MAT, San Jose, CA) in positive and negative mode, using liquid secondary ionization (LSIMS) with a Cs ion beam at 20 keV.

General Method for Preparation of Halide Salts

In a dry, three necked, round-bottomed flask, equipped with magnetic stirrer were added 50% w/w of CH_3CN , CH_2X_2 , where $\text{X} = \text{Cl}, \text{Br}$ or I (4

equivalents), amine (1 equivalent) and a few crystals of hydroquinone. Most reactions were left to stir overnight after which the precipitated salts were removed by filtration. The salts were washed several times with ether, acetone or ethylacetate. The desired products were obtained as a white solids.

General Method for Preparation of Tetrafluoroborate Salts

A stirred solution of the silver tetrafluoroborate (1 equiv.) in MeOH was added dropwise to a suspension of the halide salt (1 equiv.) in MeOH. After the addition, the mixture was stirred for 2 hours at room temperature and then filtered in order to remove the silver halide. The filtrate was concentrated under reduced pressure to give crude tetrafluoroborate salt. The tetrafluoroborate salts were washed with ether, acetone, ethylacetate and then recrystallized in either ethanol, ethylacetate/ethanol or water.

General Methods for Radical Reactions

A stock solution of the ammonium salt in methanol- d_4 /benzene- d_6 was made in a volumetric flask. The desired portion of the stock salt solution was placed in pyrex NMR tubes after which the appropriate amount of radical reducing agent is added. The NMR tubes were sealed with rubber septa and further secured by Teflon tape. All tubes were then cooled in a dry ice/isopropanol bath. Oxygen was removed from the tubes by using the 'freeze-thaw' method, (i.e. after freezing the tubes, a vacuum was used to pump away oxygen after which the tubes were warmed to room temperature, and the process repeated three times). For photochemical reactions, the tubes were

subjected to ultraviolet irradiation at 254nm. For thermal reactions, the tubes were heated in an oilbath. All samples were analyzed by proton NMR on the Varian Gem 300MHz spectrometer.

General Procedure for the Determination of Rates of Dealkylation of Ammonium Salts

A stock solution (~25mM) of the salt in acetonitrile- d_3 was made with benzene included as an internal standard for concentration. In sealed pyrex NMR tubes, 0.7ml of the reaction mixture was heated at the appropriate temperature. (**Note** for reactions below 80°C, the tubes were heated in a Varian Gemini 300 spectrometer which was calibrated using neat ethylene glycol as a reference. For reactions above 100 °C, the tubes were heated in a constant temperature oilbath and cooled in a dry ice/isopropanol bath immediately after removal from the oilbath in order to quench the reaction.) The disappearance of the starting materials with respect to time was monitored by proton NMR at 300MHz. In general, the reactions were not allowed to proceed beyond 50% completion. Rate constants were obtained by plotting the natural logarithm of the concentration (NMR intensity) of the salt with respect to time in seconds. Observed rates of dealkylation was obtained from the slope of the plot. The observed rates were converted to bimolecular rate constants (k_{actual}) by using the following equation:

$$k_{\text{actual}} = k_{\text{observed}}[\text{iodide salt}]^{-1}. \quad (5-1)$$

The Arrhenius parameters were determined by obtaining dealkylation rate constants at three different temperatures, and plotting the logarithm of these

rate constants against the reciprocal of the corresponding temperature in Kelvin.

All plots for the kinetic studies were obtained from Cricket Graph and errors of the measurements were interpreted from a QBasic program.

5.2 Experimental for Chapter 2

Syntheses of Precursors

Bromomethylpyridinium Bromide

A 3-necked, 500ml-round bottom flask, fitted with a spiral condenser, nitrogen tee and magnetic stirrer was flushed with nitrogen gas for 30min. The flask was then charged with 549.4g, (3.161mol) of dibromomethane after which 5.00g (63.2mmol) of pyridine was added with stirring. The reaction mixture was heated at 75°C for 23h. After cooling to room temperature, the solid product was filtered through a glass frit. After recrystallization from acetonitrile, the title compound was obtained in 56.8% yield. m.p. 218-220°C (decomp). ¹H (DMSO-d₆) δ 9.36 (d, J = 5.70Hz, 2H), 8.77 (t, J = 7.80Hz, 1H), 8.27 (t, J = 7.20Hz, 2H), 6.58 (s, 2H). ¹³C (DMSO-d₆) 148.01, 145.30, 128.83, 50.69. HRMS (LSIMS POS) calcd for C₆H₁₀NBr, 173.9742: found, 173.9724.

Bromomethylpyridinium Tetrafluoroborate. 2-32.

Into a 50ml-round bottom flask containing 10ml of methanol was added 2.00g of bromomethylpyridinium bromide. Using a pipet, a solution of silver tetrafluoroborate (1.70g, 8.81mmol) in 9ml of methanol was added to the salt solution in a dropwise manner with stirring. The reaction mixture was stirred for 1.5h at room temperature. The precipitated silver bromide was filtered from the

reaction mixture through Celite and the filtrate was condensed by rotary evaporation. The residue was recrystallized from absolute ethanol to give the title compound in 70.5% yield. m.p. 108-110°C. ^1H (DMSO- d_6) δ 9.35 (d, J = 6.0Hz, 2H) 8.77 (t, J = 7.8Hz, 1H) 8.23 (t, J = 7.8Hz, 2H) 6.55 (s, 2H). ^{13}C (DMSO- d_6) 148.07, 145.32, 128.90, 50.74. HRMS (LSIMS POS) calcd for $\text{C}_6\text{H}_7\text{NBr}$, 173.9742: found, 173.9738; CHN analysis calcd for $\text{C}_6\text{H}_7\text{NBr}$: C, 27.735, H, 2.716, N, 5.391: found C, 27.430, H, 2.649, N, 5.177.

Dimethylaminomethyl phenyl sulfide

A 3-necked, 100ml- round bottom flask was fitted with a 25ml pressure-equalizing addition funnel, spiral condenser, ice bath and magnetic stirrer. Into the flask was added 22ml (0.17mol) of 40% dimethylamine solution. Thiophenol (20.5ml, 0.200mol) was added to the cooled amine over 30min. To the resulting mixture was added 14.1g (0.173mol) of 37% formaldehyde solution in water. The reaction mixture was heated at room temperature for 30min before raising the temperature to 80°C where it was heated for 2h. The reaction mixture was cooled to room temperature and afterwards extracted three times with 25ml portions of diethyl ether. The combined ether extract was dried with anhydrous sodium sulfate. After filtering the drying agent through a glass frit, the ether was removed by rotary evaporation. The residue was then fractionally distilled through a 2" vigreux at 53-55°C at 0.15mm. The title compound was obtained in 78% yield. ^1H (CDCl_3) δ 7.33 (m, 5H) 4.45 (s, 2H) 2.29 (s, 6H). ^{13}C (CDCl_3) 137.88, 131.41, 128.77, 126.84, 68.63, 42.37. HRMS (LSIMS POS) calcd for $\text{C}_9\text{H}_{14}\text{NS}$, 168.0847: found, 168.0847.

Benzyl thiomethyl dimethylammonium Chloride, 2-35

A 100ml round bottom flask was charged with 18ml of benzene. To the flask was added 6.39g (0.0431mol) of dimethylaminomethyl phenyl sulfide and 5.49g (0.0431mol) of benzyl chloride. The reaction mixture was stirred at room temperature for 17hr. To the reaction mixture was added 40ml of diethylether after which the 'oily' product solidified and precipitated out of solution. The solid was filtered from the reaction mixture through a glass frit. The filtrate was then heated at 60°C for 1.5h to produce more product. Both batches of the solid were combined and recrystallized from a 2:3 mixture of ethyl acetate/chloroform. The title compound was obtained in 55% yield. m.p. 170-171°C. ¹H (DMSO-d₆) δ 7.59 (m, 10H), 5.14 (s, 2H), 4.64 (s, 2H), 2.92 (s, 6H). ¹³C (DMSO-d₆) 133.02, 132.32, 131.09, 130.30, 129.68, 128.90, 128.43, 127.83, 68.17, 65.28, 47.89. HRMS (LSIMS POS) calcd for C₁₆H₂₀NS, 258.1317: found, 258.1311.

Benzylthiomethyl dimethylammonium Tetrafluoroborate, 2-36

Into a 25ml round bottom flask fitted with a magnetic stirrer was weighed 0.879g (4.52mmol) silver tetrafluoroborate. To the flask was added 7ml methanol to dissolve the silver salt. A solution of 1.33g (4.51mmol) benzylthiomethyl dimethyl-ammonium chloride in 7ml methanol was added to the tetrafluoroborate solution over 1.3h. The reaction was stirred at room temperature for 16.5h after which time, silver chloride was filtered from the reaction mixture. The filtrate was concentrated by rotary evaporation to give an oily residue which solidified after scratching. After recrystallization from ethanol, the title compound was obtained in 78% yield. m.p. 86-88°C. δ 7.59 (m, 10H), 5.14 (s, 2H), 4.64 (s, 2H), 2.92 (s, 6H). ¹³C (DMSO-d₆) 132.94, 132.268,

131.48, 130.40, 129.76, 129.02, 128.70, 127.56, 68.82, 65.70, 48.11. HRMS (LSIMS POS) calcd for $C_{16}H_{20}NS$, 258.1316: found, 258.1310.

N-Benzyl-N, N,N-trimethylammonium Tetrafluoroborate, 2-37

A 3-necked, 25ml round bottom flask fitted with a pressure-equalizing addition funnel, a magnetic stirrer, rubber septa, and a nitrogen tee was flushed with nitrogen for 1h. To the flask was added 10ml methylene chloride foiled by 1.204g (8.141mmol) of trimethyloxonium tetrafluoroborate. Via the addition funnel, 1.00g (7.40mmol) of N-benzyl-N,N-dimethylamine was added to the reaction vessel over 30min. The reaction was exothermic. It was allowed to stir at room temperature for 17h after which the solvent was removed by rotary evaporation. The solid residue was subjected to full vacuum for 3h after which time it was recrystallized from absolute ethanol to yield the title compound as a white crystalline solid in 71.9% yield. m.p. 125-127°C. ^1H (DMSO- d_6) δ 7.54(m, 5H) 4.52 (s, 2H) 3.03 (s, 9H). ^{13}C (DMSO- d_6) 132.78, 130.33, 128.95, 128.28, 67.86, 51.73. HRMS (LSIMS POS) calcd for $C_{10}H_{16}N$, 150.1283: found, 150.1245.

N-Allyl-N, N-Dimethylamine

A 500ml-, 3-necked, round bottom flask was fitted with a dry ice condenser, dry ice/isopropanol bath, a 250ml pressure equalizing addition funnel, rubber septa, and a magnetic stirrer. Into the cooled flask was condensed 250ml of dimethylamine gas. The amine was then dissolved in 100ml of diethyl ether. Over a 2h period, 10.0g (0.0827mol) of allylbromide was added to the amine solution with stirring. The reaction mixture was allowed to

stir at -60°C for 1h after which it was stirred at room temperature overnight for 18hr. To the reaction mixture was added 3.31g (0.0830mol) of solid sodium hydroxide. The allyl-substituted amine was fractionally distilled through a 15cm vigreux and was obtained as an azeotrope in diethyl ether (35% yield). b.p. 45-52°C. ^1H (CDCl₃) δ 2.22 (s, 6H), 2.98 (d, J = 6.6Hz, 2H), 5.12 (dd, J = 8.40Hz, J = 1.50Hz, 1H), 5.18 (dd, J = 17.10Hz, J = 1.5Hz, 1H), 5.86 (ddt, J = 17.10Hz, J = 10.20Hz, J = 6.60Hz, 1H).

N-Allyl-N-Iodomethyl-N, N-Dimethylammonium Iodide 2-41

The title compound was synthesized in 38% yield when 1.00g (11.7mmol) of allyl-N, N-dimethylamine was reacted with 9.44g (0.353mol) of diiodomethane in 6ml of acetonitrile, using the general procedure for the synthesis of iodide salts. m.p. 101-104°C ^1H NMR (DMSO-d₆) δ 3.11 (s, 6H), 4.05 (d, J = 7.2Hz, 2H), 5.11, (s, 2H), 5.68 (m, 2H), 6.00 (m, 1H); ^{13}C NMR (DMSO-d₆) 33.07, 50.88, 66.09, 125.40, 128.294; HRMS (LSIMS POS) calcd for C₆H₁₃NI: 226.0093; found, 226.0095. CHN analysis calcd for C₆H₁₃NI₂: C, 20.416, H, 3.712, N, 3.968; found C, 20.582, H, 3.688, N, 3.909

Iodomethyl-trimethylammonium Tetrafluoroborate (2-1)

The title compound was prepared from 3-4 (3.3 g, 0.010 mol) following the general method described above. Recrystallization from ethanol gave 2-1 (2.28 g, 80%) as a white solid, m.p 110-112°C, ^1H NMR (DMSO-d₆) δ 3.18 (s, 9H), 5.21 (s, 2H); ^{13}C NMR (DMSO-d₆) 34.00, 53.09.; HRMS(LSIMS POS) calcd for C₄H₁₁N⁺I, 199.9935, found 199.9934. Anal. calcd for C₄H₁₁NIBF₄: C, 16.75; H, 3.86; N, 4.88; found C, 16.884; H, 3.748; N, 4.673.

Distonic Radical Reactions

Reduction of Pyridinio Distonic Radical Cation

As described in the general procedure for the radical reactions, 0.5015g (1.923mmol) of **2-23** was dissolved in 10ml of a 2:3 mixture of acetonitrile and benzene. To the solution was added 1.294ml of tributyltin hydride. The reaction mixture was then transferred to a pyrex test tube which was then sealed with a rubber septum and teflon tape. The reaction mixture was then degassed and then irradiated for 2h. After filtering the tributyltinbromide that had formed in the reaction, the filtrate was condensed by rotary evaporation to give the product as an oil. Proton NMR analysis of the oil showed no signs of the starting material. The product was determined to be methylpyridinium tetrafluoroborate. ^1H NMR (DMSO-d_6) δ 8.94 (d, $J = 5.76\text{Hz}$, 2H), 8.56 (t, $J = 7.70\text{Hz}$, 1H), 8.11 (t, $J = 6.89\text{Hz}$, 2H) 4.39 (s, 3H).

Attempt to React **2-32** with Alkenes

The reaction mixtures were prepared using the procedure described for general radical reactions. In each case, the alkenes were added in ten-fold excess of the pyridinium salt, **2-32**. The alkenes used were styrene, α -methylstyrene, and ethylvinyl ether. Upon irradiating the reaction mixtures, no addition of the alkenes were detected by proton NMR. Instead, only polymerization of the alkenes were detected.

Phenylthiomethyl trimethylammonium Iodide

In a 10ml round bottom flask was placed 0.559g (2.99mmol) of dimethylaminomethyl phenyl sulfide, 0.85g (5.99mmol) methyl iodide and 5ml acetonitrile. The reaction mixture was stirred at room temperature for 17h. The crude product was filtered from the reaction mixture through a glass frit and recrystallized from absolute ethanol. The title compound was obtained as a white solid in 20% yield. m.p. 152-153, ^1H (DMSO- d_6) δ 3.07 (s, 6H), 5.11 (s, 2H), 7.44 (m, 3H), 7.70 (d, $J = 6.59$ Hz, 2H). ^{13}C (DMSO- d_6) 51.20, 69.32, 128.51, 129.66, 131.18, 132.08. HRMS (LSIMS POS) calcd for $\text{C}_{10}\text{H}_{16}\text{NS}$, 182.1004: found, 182.002.

Cyclic Voltammetry

Table 5-1. Peak Potentials for the first cyclic voltammetric reduction wave of various iodides in acetonitrile at the gc electrode vs. SCE using Bu_4NPF_6 as the supporting electrolyte.

Substrate	Peak Potential @ 0.25V/s (V)	$k_H/10^6$ ($\text{M}^{-1}\text{s}^{-1}$)
$\text{Me}_3\text{N}^+\text{CH}_2\text{I BF}_4^-$, 2-1	-1.39	6.0
$\text{C}_7\text{F}_{15}\text{I}$, 2-46	-1.19	200
$\text{CF}_3\text{CH}_2\text{I}$, 2-47	-1.80	--
$\text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2\text{I}$, 2-48	-2.0	2.1

The cyclic voltammetry experiments were performed in a BAS CV-27 potentiostat. The working electrode was a glassy carbon electrode, the counter electrode was a platinum electrode and the reference electrode was a Ag/AgCl

electrode. Tetrabutylammonium hexafluorophosphate (Bu_4NPF_6) was in 0.1M concentration in anhydrous acetonitrile was used as the supporting electrolyte.

Using the supporting electrolyte as solvent, 3mM solutions of each substrate were prepared in 5ml volumetric flasks. Electrolyses were performed in a two-compartment cell at a scan rate of 250mV/s within a range of -2000mV and 1500mV. Results from the electrochemical experiments are shown in Table 5-1.

Average Kinetic Isotope Effect (KIE) for the reduction of 2-1

Table 5-2. Volumes of nBu_3SnH and nBu_3SnD used in KIE study of 2-1

Tube #	Vol nBu_3SnH (ml)	Vol nBu_3SnD (ml)
1	60	40
2	55	45
3	50	50
4	45	55
5	40	60
6	35	65

Into six pyrex NMR tubes was placed 0.6ml aliquots of 20.2mM solution of 2-1 in a 1:1 mixture of methanol- d_4 and benzene- d_6 . The amounts of tributyltin hydride and tributyltin deuteride that was added to each tube is shown in Table 5-2. Each tube was sealed with a rubber septum and further secured with Teflon tape. The tubes were de-gassed using the 'freeze-thaw' method. All tubes were irradiated for 1.5h. The contents of each tube were transferred to six separate 5ml- pear shaped flasks. The volatiles were removed from each

reaction mixture using a full vacuum. The non-volatile residues were washed once with 1ml portions of benzene. After centrifugation of the benzene wash, the benzene was decanted and the solid residues were dried with a slow stream of nitrogen gas. The residue from each tube was labeled separately and analyzed by mass spectral analysis which gave the relative abundances of molecular ions 74 (**2-3**) and 75 (**2-45**) (Table 5-3).

Table 5-3. Data for determining the KIE of the reduction of **2-1**.

[2-3]/[2-45]	[nBu₃SnH]/[nBu₃SnD]
2.4	1.50
2.1	1.20
1.7	1.00
1.4	0.82
1.1	0.67
0.9	0.54

5.3 Experimental for Chapter 3

Syntheses of Precursors

N-Benzyl-N, N, N-Trimethylammonium Iodide

To a 25ml-round bottom flask containing 8ml of diethyl ether was added 1.75ml (3.97g, 28.0mmol) of methyl iodide. To the solution was added 1g (9.33mmol) of dimethylbenzylamine with stirring at room temperature. After 1h, the exothermic reaction yielded 1.75g (76.0%) of the title product as a white

solid. m.p. 180 - 181°C, ^1H (DMSO- d_6) δ 3.04 (s, 9H), 4.56 (s, 2H), 7.55 (s, 5H). ^{13}C (DMSO- d_6) 51.66, 67.44, 128.22, 128.80, 130.20, 132.69

Dibenzyl-N, N-Dimethylammonium Iodide, 3-8

The title compound was made using the general procedure for the synthesis of the iodide salts. The salt was obtained in 80.9% yield. m.p. 185°C (decomp) ^1H (DMSO- d_6) δ 2.91 (s, 6H), 4.72 (s, 4H), 7.59 (m, 10H). ^{13}C (DMSO- d_6) 48.05, 66.76, 127.86, 128.85, 130.24, 133.05. HRMS (LSIMS POS) calcd for $\text{C}_{16}\text{H}_{20}\text{N}$: 226.1596; found 226.1577

bis-Cinnamyl-N, N-Dimethylammonium Iodide, 3-10

Using the general procedure for the synthesis of iodide salts, the title salt was obtained in 84.5% yield. m.p. 170°C (decomp) ^1H (DMSO- d_6) δ 3.11 (s, 6H), 4.22 (d, $J = 7.41\text{Hz}$, 4H), 6.58 (dt, $J = 15.65\text{Hz}$, 2H), 6.98 (d, $J = 15.66\text{Hz}$, 2H), 7.38 (m, 6H), 7.63 (d, $J = 6.87$, 2H). ^{13}C (DMSO- d_6) 49.09, 64.83, 116.77, 127.18, 128.62, 128.83, 135.28, 140.78. HRMS (LSIMS POS) calcd for $\text{C}_{20}\text{H}_{24}\text{N}$, 278.1909; found, 278.1910.

N-Iodomethyl-N, N, N-trimethylammonium Iodide, 3-4

The title compound was prepared by the general method described above. The trimethylamine (7.4g, 0.125 mol) was bubbled slowly into the diiodomethane solution. The desired product was obtained as a white solid in 95.9% yield. m.p. 235°C (decomp), ^1H NMR (DMSO- d_6) δ 3.22 (s, 9H), 5.24 (s, 2H); ^{13}C NMR (DMSO- d_6) 34.80, 53.13.

N-Bromomethyl-N, N, N-Trimethylammonium Tetrafluoroborate, 3-11

The title compound was synthesized in 90.4% yield when 1.00g (5.47mmol) of the bromide was reacted with one equivalent of silver tetrafluoroborate (1.07g, 5.47mmol) following the general procedure for the synthesis of tetrafluoroborate salts. m.p. 166 - 167°C ^1H NMR (DMSO- d_6) δ 3.19 (s, 9H), 5.31 (s, 2H); ^{13}C NMR (DMSO- d_6) 51.84, 59.06. HRMS (LSIMS POS) calcd for $\text{C}_4\text{H}_{11}\text{NBr}$: 152.0075; found, 152.0019. CHN analysis calcd for $\text{C}_4\text{H}_{11}\text{NBrBF}_4$: C, 20.031, H, 4.623, N, 5.840; found: C, 20.233, H, 4.617, N, 5.759

N-Chloromethyl-N, N, N-Trimethylammonium Tetrafluoroborate, 3-12

The title compound was obtained in 89.9% yield when 1.00g (7.00mmol) of the chloride was reacted with 1.36g (7.00mmol) of silver tetrafluoroborate in 10ml of acetonitrile. The crude product was recrystallized from 6:1 ethanol/acetonitrile solvent mixture. m.p. 221-224°C ^1H NMR (DMSO- d_6) δ 3.18 (s, 9H), 5.35 (s, 2H); ^{13}C NMR (DMSO- d_6) 42.36, 47.13 HRMS (LSIMS POS) calcd for $\text{C}_4\text{H}_{11}\text{NCl}$: 108.0580; found, 108.0575; CHN analysis calcd for $\text{C}_4\text{H}_{11}\text{NClBF}_4$: C, 24.588, H, 5.675, N, 7.169; found C, 24.553, H, 5.568, N, 7.035

N-Chloromethyl-N, N, N-trimethylammonium Chloride, 3-14

Into a gas sampling tube that was cooled to -78°C, was weighed 3.12g (52.8mmol) of trimethylamine gas. The amine was then dissolved with 10ml

acetonitrile and the resulting solution transferred to a 50ml-, 3-necked, round bottom flask fitted with a magnetic stirrer and a 25ml-pressure-equalizing addition funnel. To the flask was added 11.9ml (13.5g, 158mmol) of dichloromethane in 7ml acetonitrile over 4h. The reaction was stirred at -78°C for 5hr and then allowed to warm up to room temperature over 19h, with stirring. The white ammonium chloride salt, which was hygroscopic in nature, was filtered from the reaction mixture under nitrogen atmosphere, and then washed with three 10ml portions of diethyl ether. The crude product was isolated in 44.3% yield. m.p. 150-153°C, ^1H NMR (DMSO- d_6) δ 3.27 (s, 9H), 5.62 (s, 2H). ^{12}C (DMSO- d_6) 50.64, 69.63. HRMS (LSIMS POS) calcd for $\text{C}_4\text{H}_{11}\text{N}_1^+\text{Cl}$: 108.0580; found 108.0552

N-Bromomethyl-N, N, N-Trimethylammonium Bromide, 3-13

The title compound was synthesized using the same methodology described for the synthesis of the iodide salts. One equivalent of trimethylamine gas was reacted with three equivalents of dibromomethane to give the bromide salt in 92.7% yield after recrystallization in absolute ethanol. mp 165-166°C, ^1H NMR (DMSO- d_6) δ 3.32 (s, 9H), 5.61 (s, 2H). ^{12}C (DMSO- d_6) 51.58, 59.05

N-Cinnamyl-N, N-Dimethylamine

A 50ml-, 3-necked round bottom flask fitted with a pressure-equalizing addition funnel, septa, a glass stopper, magnetic stirrer and a nitrogen tee was flushed with nitrogen for 1h. To the flask was added 14 ml of dimethylamine solution, (40% wt. in water). A solution containing 1g (5.09 mmol) cinnammyl bromide in 10ml THF was added to the flask over a 30min period with stirring.

The reaction was stirred at room temperature for 1h. The THF and excess dimethylamine were then removed under reduced pressure after which 20ml of diethylether was added. The organic layer was separated and extracted with 15ml of 10% hydrochloric acid. The acidic extract was then treated with 10ml 2N sodium hydroxide solution after which it was extracted three time with 20ml portions of ether. The ether solution was then dried with anhydrous sodium sulfate, filtered and concentrated by rotary evaporation. The oily residue solidified upon refrigeration. The solid amine was produced in 72.7% yield. m.p. 28-29°C ^1H (CDCl_3) δ 2.35 (s, 6H), 3.18 (d, J = 6.59Hz, 2H), 6.29 (dt, J = 6.59Hz, J = 15.93Hz, 1H), 6.55 (d, J = 15.93Hz, 1H); ^{13}C (CDCl_3) 45.21, 62.04. 126.29, 127.31, 127.38, 128.51, 132.59, 137.02. HRMS (LSIMS POS) ($M+1$) calcd for $\text{C}_{11}\text{H}_{16}\text{N}$: 162.1283; found, 162.1279

Determination of the Rate of Demethylation of 3-4

Table 5-4. Data for determining the rate of de-methylation of 3-4.

65°C	time (s)	0.00	7200	14400	21600	28800	36000
	$\ln[\text{SM}]^{(a)}$	0.00	-0.04	-0.09	-0.12	-0.15	-0.19
70°C	time (s)	0.00	7200	14400	21600	28800	36000
	$\ln[\text{SM}]^{(a)}$	0.00	-0.05	-0.10	-0.18	-0.22	-0.29
75°C	time (s)	0.00	3600	7200	10800	14400	21600
	$\ln[\text{SM}]^{(a)}$	0.00	-0.05	-0.10	-0.15	-0.21	-0.29

(a) $[\text{SM}]$ = concentration of starting material, 3-4, based on NMR integration

As in the case of 2-37, 20mM solutions of 3-4 in deuterated acetonitrile were heated in the Varian Gemini 300 spectrometer at 65°C, 70°C, and 75°C,

and the disappearance of the starting material (i.e. methyl peak at δ 3.3ppm) was monitored by proton NMR with respect to time. The data obtained from each kinetic experiment is shown in Table 5-4. The rate constants for the demethylation of **3-4** are summarized in Table 5-5. Formation of methyl iodide was verified by adding commercially available methyl iodide to the reaction mixture and observing the growth of the corresponding peak (δ 2.2ppm).

Table 5-5. Rate constants for the demethylation of **3-4**.

Temperature ($^{\circ}\text{C}$)	Rate constant ($\text{M}^{-1}\text{s}^{-1}$)
65	$2.8 (\pm 0.1) \times 10^{-4}$
70	$4.1 (\pm 0.2) \times 10^{-4}$
75	$6.6 (\pm 0.2) \times 10^{-4}$

The Arrhenius parameters was determined using the same method used for **2-37**. The energy of activation was determined to be $19.0 (\pm 0.3) \text{ kcal M}^{-1}\text{K}^{-1}$ and the log A was $8.7(\pm 0.2)$ with $\Delta S^{\ddagger} = -18.0 \text{ cal mol}^{-1}$.

Determination of the Rates of Demethylation of **3-11**.

Reaction with one equivalent of Iodide

A solution of 0.0167mmol of **3-11** and 0.0167mmol benzyltrimethylammonium iodide in 0.7ml acetonitrile- d_3 was heated in a constant temperature oilbath at 101°C for ten minute intervals for a period of 60min. The disappearance of the bromide salt was monitored by observing the decrease of its methyl peak at δ 3.22ppm with respect to time. The proton signal for the methyl peak in the iodide salt, δ 3.03ppm, was used as an internal standard (Table5-6). A second order rate constant was obtained from the slope

of a plot of the reciprocal of the concentration of the bromide salt (based on proton integration) against time. The rate constant was found to be $1.87 (0.08) \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$.

Table 5-6. Data for determining the rate of de-methylation of **3-11** with one equivalent of iodide.

[3-11]	[3-11] ⁻¹	t (s)
19.47	0.0514	0
16.54	0.0605	600
14.52	0.0689	1200
12.11	0.0826	1800
10.64	0.0940	2400
9.35	0.1070	3000

Reaction with two equivalents of iodide

Table 5-7. Data for determining the rate of de-methylation of **3-11** with two equivalent of iodide.

$\ln \{1 + ([\text{sm}]_0 / [\text{sm}])\}^{(a)}$	time (s)
0.693	0
0.816	600
0.934	1200
1.149	2400
1.200	3000

^(a) [sm] = concentration of starting material, **3-11**, as indicated by ¹H NMR peak intensity

Into 10ml volumetric flask was weighed 0.0459g (0.1913mmol) of **3-11** and 0.0955g (0.3834mmol) of the iodide salt. The salts were dissolved with 10ml of deuterated acetonitrile. Using 500 μ l and 200 μ l syringes, 0.7ml aliquots of the stock solution were placed in 5 pyrex NMR tubes. Each tube was sealed with a flame and then heated in a constant temperature oilbath at 101°C. Each tube was removed from the oilbath after at least six minutes, cooled to -78°C, and the contents analyzed by proton NMR. The data for this experiment is shown in Table 5-7.

Determination of the Rate of Demethylation of **3-12**

The rate for de-methylation was determined using the same methodology used for **3-11**. The equimolar solution of **3-12** and benzyltrimethylammonium iodide was heated at 101°C for 30min intervals. The second order rate constant for the demethylation of **3-12** was found to be 4.79 (0.07) $\times 10^{-6} \text{ M}^{-1} \text{ s}^{-1}$.

Table 5-8. Data for determining the rate of de-methylation of **3-12** with one equivalent of iodide.

[3-12]	[3-12]⁻¹	time (s)
19.47	0.0514	0
16.54	0.0605	600
14.52	0.0689	1200
12.11	0.0826	1800
10.64	0.0940	2400
9.35	0.1070	3000

N-Iodomethyl-N, N, N-triethylammonium Iodide

The title compound was synthesized using the general method described for synthesizing halide salts. Triethylamine (2.0g, 0.0198 mol) and diiodomethane (15.9g, 0.0593mol) were stirred together in 20ml of ethyl acetate at room temperature for 48hr. The desired product was filtered from the reaction mixture through a glass frit and isolated in 47.7% yield (3.48g) after recrystallization from absolute ethanol. m.p. 178°C (decomp), ^1H NMR (DMSO- d_6) δ 1.21 (t, J = 7.14Hz, 9H), 3.34 (q, J = 7.15H, 6H), 5.1 (s, 2H); ^{13}C NMR (DMSO- d_6) 7.74, 27.86, 53.93. HRMS (LSIMS POS) calcd for $\text{C}_7\text{H}_{17}\text{NI}$, 242.0406: found, 242.0398

N-Iodomethyl-N, N, diethyl-N-methylammonium Iodide

A 25ml-round bottom flask fitted with a magnetic stirrer was charged with 10ml of ethyl acetate. The flask was sealed with a rubber septum. Via syringe, 3ml of diethylmethyl amine (2.16g, 0.0248mol) was added followed by 3.03g (0.0113mol) of diiodomethane with stirring. The reaction mixture was stirred at room temperature for 18h before adding an addition 10ml of the amine. The stirring was allowed to continue for an additional 24h period. The solid product was filtered from the reaction mixture through a glass frit and later recrystallized from absolute ethanol. The product was dried under full vacuum and was isolated in 9.2% (0.37g). m.p. 146-147.5°C, ^1H NMR (DMSO- d_6) δ 1.23 (t, J = 7.15Hz, 6H), 3.04 (s, 3H), 3.41 (m, 4H), 5.1 (s, 2H); ^{13}C NMR (DMSO- d_6) 7.91, 30.15, 47.65, 57.45. HRMS (LSIMS POS) calcd for $\text{C}_6\text{H}_{15}\text{NI}$, 228.0249: found, 228.0256.

N-Iodomethyl-N-ethyl-N, N-dimethylammonium Iodide

The synthesis was the same as for the diethyl analog. In this reaction, 1.02g of dimethylethyl amine (0.0139mol) and 5.53g (0.0206mol) of diiodomethane were stirred together in 8ml of ethyl acetate at room temperature for 25.5hr. To the reaction mixture were added 10ml extra of the amine and 5ml of ethyl acetate, after which, the reaction mixture was stirred at room temperature for an additional 24h. The solid product was filtered from the reaction mixture through a glass frit, and then recrystallized from absolute ethanol to give the pure, desired product in 36.8% yield (2.59g). m.p. 120-121.5°C; ^1H NMR (DMSO-d_6) δ 1.25 (t, $J = 7.20\text{Hz}$, 3H), 3.14 (s, 6H), 3.47 (q, $J = 7.20\text{H}$, 2H), 5.19 (s, 2H); ^{13}C NMR (DMSO-d_6) 8.16, 32.61, 50.59, 60.06. HRMS (LSIMS POS) calcd for $\text{C}_5\text{H}_{13}\text{NI}$, 214.0093; found, 214.0106.

Determination of the Rate of De-ethylation of **3-15a**

A 20mM stock solution of **3-15a** in deuterated acetonitrile with benzene as an internal standard was made. Using a gas-tight syringe, 0.7ml portions of the stock solution were added to seven NMR tubes. The tubes were sealed by a torch. Six of the tubes were heated in a constant temperature oilbath at 101°C and removed at 1h intervals. The reactions were quenched by placing each tube in a dry ice/isopropanol bath. All seven tubes were analyzed by proton NMR and the disappearance of the starting material (i.e. methylene peak at δ 5.1ppm) was observed in each one. A first order rate constant was obtained from the slope of a plot of the reciprocal of the concentration of the bromide salt (based on proton integration) against time (Table 5-9). The bimolecular rate constant was found to be $2.79 (0.05) \times 10^{-3} \text{ M}^{-1}\text{s}^{-1}$. Formation of ethyl iodide was

verified by adding commercially available ethyl iodide to the reaction mixture and observing the growth of the corresponding peaks, i.e. δ 1.8ppm, 3.3ppm.

Table 5-9. Data for determining the rate of de-ethylation of **3-15a**.

$\ln\{[sm]/[sm]_0\}^{(a)}$	time (s)
0.00	0
-0.17	3900
-0.42	7260
-0.62	10860
-0.80	14400
-1.00	18000
-1.23	21900

^(a) [sm] concentration of **3-15a** as indicated by ^1H NMR peak intensity

Determination of the Absolute Rate of De-Alkylation of **3-15b**

The same procedure used for the triethyl analog was applied. The reactions were performed using a 21mM stock solution of the diethyl salt. Six tubes, each containing 0.7mL of the stock solution, were heated at 101°C and were removed at 30min intervals. Each tube was analyzed by proton NMR and the disappearance of the starting material (CH_2 , δ 4.9ppm) was monitored with respect to time (Table 5-10). The unimolecular rate constant obtained from the slope was divided by the concentration of the stock solution as shown in equation 5, to get the bimolecular rate constant. The bimolecular rate constant was determined to be $6.3 (0.3) \times 10^{-3} \text{M}^{-1} \text{s}^{-1}$.

Table 5-10. Data for determining the rate of de-alkylation of **3-15b**.

$\ln\{[sm]/[sm]_0\}^{(a)}$	time (s)
0.00	0
-0.12	2100
-0.45	3900
-0.73	5700
-0.94	7500
-1.40	11100

^(a) [sm] concentration of **3-15b** as indicated by ¹H NMR peak intensity

Determination of the relative rate of de-methylation to de-ethylation in **3-15b**

Table 5-11. Data for determining the relative rate of de-methylation and de-ethylation of **3-15b**.

[MeI]	[EtI]	[MeI]/[EtI]	time (s)
3.60	0.88	4.09	1800
7.09	2.25	3.15	3600
9.38	3.20	2.93	6000
10.81	4.85	2.23	7200
12.20	3.71	3.29	9000
13.40	4.94	2.71	10800

The kinetic experiment described for obtaining the rate of de-alkylation of **3-15b** was repeated with points being obtained at 30 min intervals. The growth of methyl iodide (singlet at δ 2.18 ppm) and ethyl iodide (triplet, CH₃, at δ 1.8

ppm) were observed (Table 5-11). The average of the points after 2h were used for the relative rate of de-methylation to de-ethylation.

Determination of the Absolute Rate of De-Alkylation of 3-15c

This reaction was performed in the same manner as the diethyl analog. The concentration of the stock solution of the ethyldimethylammonium salt was 21 mM. The reaction was performed at 101 °C and the loss of the starting material was monitored at 30 min intervals (Table 5-12). The bimolecular rate constant was determined to be $1.26 (0.04) \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$.

Table 5-12. Data for determining the rate of de-alkylation of 3-15c.

$\ln\{[\text{sm}]/[\text{sm}]_0\}^{(a)}$	time (s)
0.00	0
-0.13	600
-0.47	1800
-0.73	3000
-0.94	3600
-1.11	4200

^(a) [sm] concentration of 3-15c as indicated by ¹H NMR peak intensity

Determination of the relative rate of de-methylation to de-ethylation in 3-15c

The kinetic experiment described for obtaining the rate of de-alkylation of 3-15c was repeated with points being obtained at 30 min intervals. The same procedure that was used for 3-15b was employed in this case (Table 5-13).

Table 5-13. Data for determining the relative rate of de-methylation and de-ethylation of **3-15c**.

[MeI]	[EtI]	[MeI]/[EtI]	time (s)
8.75	0.44	19.89	1800
15.88	0.89	17.84	3600
18.91	0.64	29.55	6000
21.00	1.46	14.38	7200
22.01	1.56	14.11	9000
23.34	1.80	12.97	10800

Determination of the Rate of De-allylation of **2-37**

Table 5-14. Data for determining the rate of de-allylation of **2-37**.

40°C	time (s)	0	1800	3600	5400	6600	9600
	lg[SM] ^(a)	0.00	-0.006	-0.012	-0.021	-0.028	-0.046
50°C	time (s)	0	960	2880	3840	4800	6720
	lg[SM] ^(a)	0.00	-0.019	-0.041	-0.071	-0.082	-0.117
70°C	time (s)	0	480	960	1440	1920	2400
	lg[SM] ^(a)	0.00	-0.070	-0.152	-0.234	-0.313	-0.411

(a) [SM] = concentration of starting material, **2-37**, based on NMR integration

Rate constants for the de-allylation of 25mM **2-37** were determined at 40°C, 50°C, and 70°C, using the method described above. The spectra were recorded on a Varian Gemini 300 spectrometer. Spectra were collected in 64 transients, every 10min for 2h. The acquisition time was 2s per transient. The disappearance of the starting material was monitored by observing the

decrease of the methyl peak at δ 3.16ppm. The data was analyzed as described above and gave excellent first order correlation. The results from these experiments are summarized in Tables 5-14, 5-15 and 5-16.

Table 5-15. Data for determining the rate of de-allylation of **2-37** at 70°C with varying concentrations of iodide.

2.4 eq I ⁻	time (s)	0	600	1200	1800	2400	3000
	ln[SM] ^(a)	0.00	-0.21	-0.43	-0.63	-0.84	-1.06
3 eq I ⁻	time (s)	0	620	1240	1860	3100	3720
	ln[SM] ^(a)	0.00	-0.25	-0.44	-0.68	-1.18	-1.36

(a) [SM] = concentration of starting material, **2-37**, based on NMR integration

Table 5-16. Rate constants for the deallylation of **2-37**.

Temperature (°C)	Rate Constant (s ⁻¹)
40	1.10 (0.08)x10 ⁻⁵
50	4.6 (0.3)x10 ⁻⁵
70	3.91 (0.06)x10 ⁻⁴

Formation of allyl iodide and methylenedimethylammonium iodide in the reaction was verified by adding authentic samples to the reaction mixtures and observing the growth of the product peaks.

A plot of the logarithm of the rate constants against the reciprocal of the absolute temperatures gave a slope that corresponded to the product of a constant and the energy of activation (Equation 5-2).

$$\log k = \log A - E_a(\log e)R^{-1}T^{-1} \quad (5-2)$$

where k is the rate constant, A is the pre-exponential factor, E_a is the energy of activation, $e = 2.71828$, the gas constant $R = 1.987 \text{ cal K}^{-1}\text{mol}^{-1}$ and T is the temperature in Kelvin.

From Equation 5-2, E_a was calculated to be $24.9 (1.2) \text{ kcal M}^{-1}\text{K}^{-1}$. The intercept of the slope corresponded to $\log A$ which was 14.0. The change in the entropy of activation was determined from equation 3.

$$\Delta S^\ddagger = 4.576 \log (A/T) - 49.21 \quad (5-3)$$

where T is the average temperature.

From equation 5-3, $\Delta S^\ddagger$ was determined to be $3.66 \text{ cal mol}^{-1}$.

N-Methoxymethyl-N,N,N-Trimethylammonium Iodide.

Into a gas sampling bulb containing 15ml acetonitrile was condensed 1.5g (0.026mol) of trimethylamine. This solution was transferred to a 3-necked, 25ml-round bottom flask that was fitted with a 10ml pressure equalizing addition funnel. A solution of 5.1g (0.0291mol) iodomethylmethylether in 5ml acetonitrile was added to the amine solution over 1h. The reaction mixture was allowed to stir at room temperature for 26hr. To the reaction mixture was added 10ml diethyl ether after which the solid product precipitated out of solution. The title compound was obtained in 64.8% yield after recrystallization from absolute ethanol. m.p. $121-122^\circ\text{C}$. ^1H (DMSO- d_6) δ 4.63 (s, 2H), 3.63 (s, 3H) 3.01 (s, 9H). ^{13}C (DMSO- d_6) 92.64, 61.04, 48.76. HRMS (LSIMS POS) calcd for $\text{C}_5\text{H}_{14}\text{NO}$, 104.1075: found, 104.1075; CHN analysis calcd for $\text{C}_5\text{H}_{14}\text{NO}$: C, 25.989, H, 6.107, N, 6.062: found C, 25.925, H, 5.978, N, 5.988.

N-Allyl-N,N,N-Trimethylammonium Bromide.

A 3necked, 100ml-round bottom flask fitted with a magnetic stirrer and a nitrogen tee, was flushed with nitrogen for 30min. The flask was then charged with 10ml anhydrous ethyl ether. To the flask was added 1ml (1.40g, 1.16mmol) of allyl bromide after which the reaction mixture was cooled with a dry ice/isopropanol bath. A large excess of trimethylamine was bubbled into the reaction mixture and the reaction was stirred a for 1h. The solid product sublimed at room temperature.

N,N,N-Trimethylammonium Tetrafluoroborate, 2-40

In a 3necked, 25ml-round bottom flask fitted with a magnetic stirrer was placed 3.139ml (3.704g, 0.0228mol) of 54% fluoroboric acid in ether. This was further dissolved in 7ml anhydrous diethyl ether. After cooling the solution to -20°C, a large excess of trimethylamine gas was bubbled into the flask until the reaction mixture retained a cream color. The reaction mixture was stirred for 18h. The solid product was filtered and used without further purification. Crude yield: 99.1%. m.p. 80-86°C. ^1H (DMSO- d_6) δ 2.75 (s, 9H), 6.90(s, 1H) . ^{13}C (DMSO- d_6) 44.34 HRMS (LSIMS POS) calcd for $\text{C}_3\text{H}_{10}\text{N}$, 60.0813: found, 60.0765.

APPENDIX SELECTED ^1H NMR AND MASS SPECTRA

The following spectra have been included in this dissertation as they have been critical in the determination of the unusual transformations that have been described in the preceeding chapters. The spectra have been presented in the same order as discussed in Chapters 2 and 3.

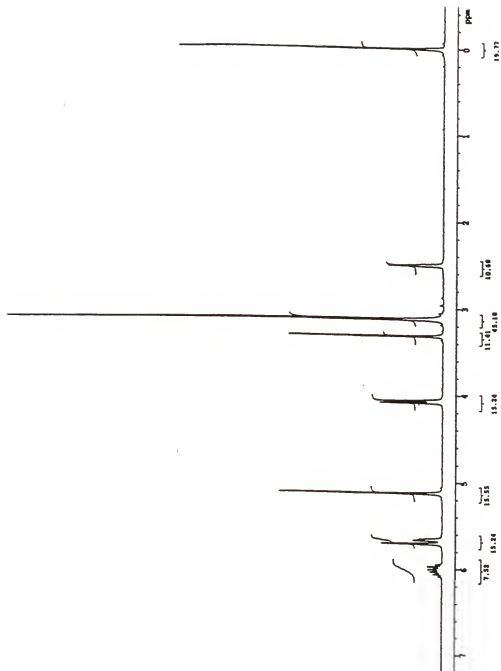


Figure A-1. ^1H NMR spectrum of Allyldimethyliodomethyl ammonium iodide, 2-37

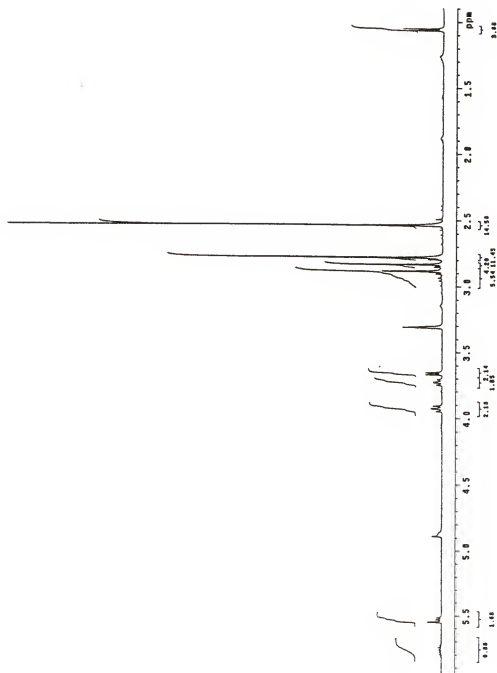


Figure A-2. ^1H NMR spectrum of the product mixture of 2-42, 2-43 and 2-44

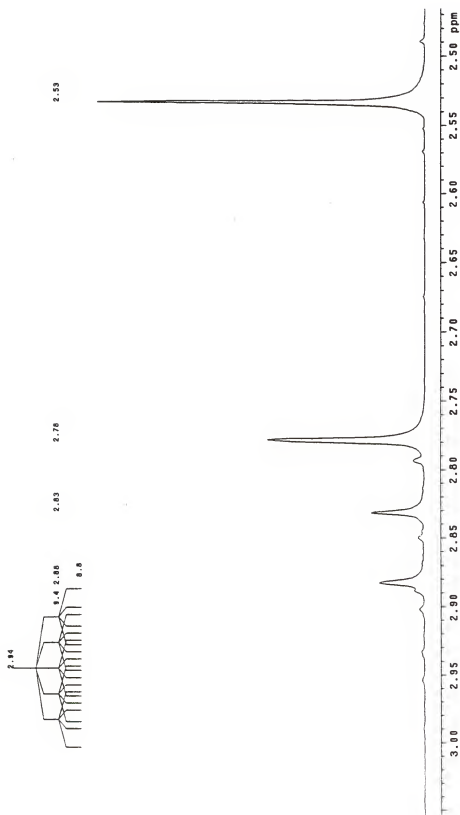


Figure A-3. Expansion of methyl region in Figure A-2.

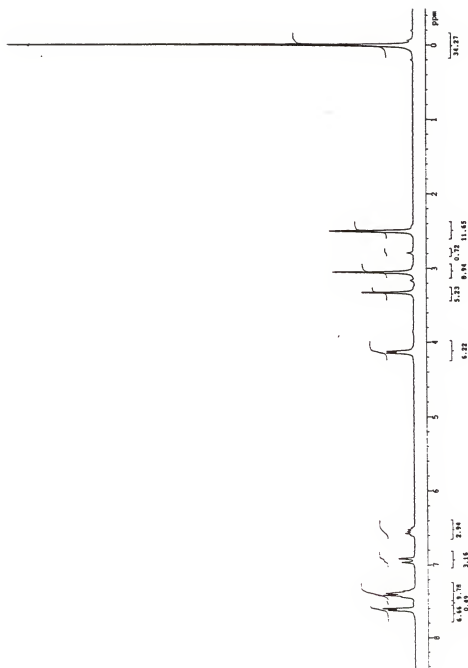


Figure A-4. ^1H NMR spectrum of bis-cinnamyl ammonium iodide, 3-10

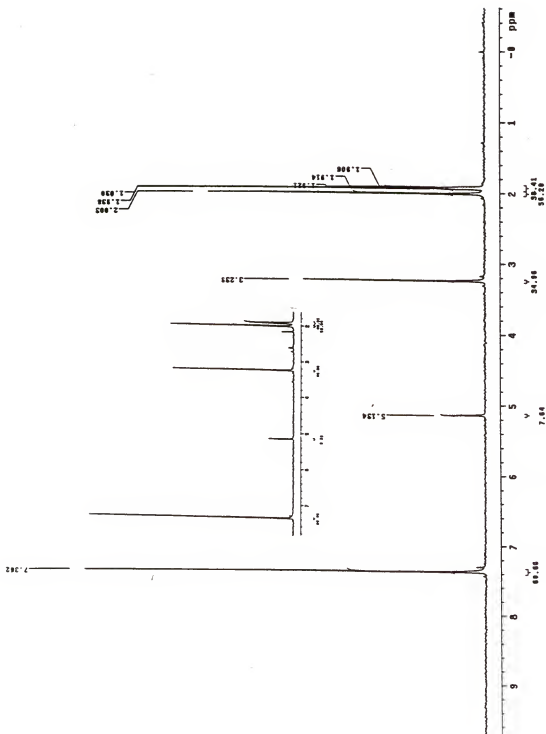


Figure A-5. De-methylation of 3-4 at 65°C. (a) $t = 0$ h; (b) $t = 13$ h

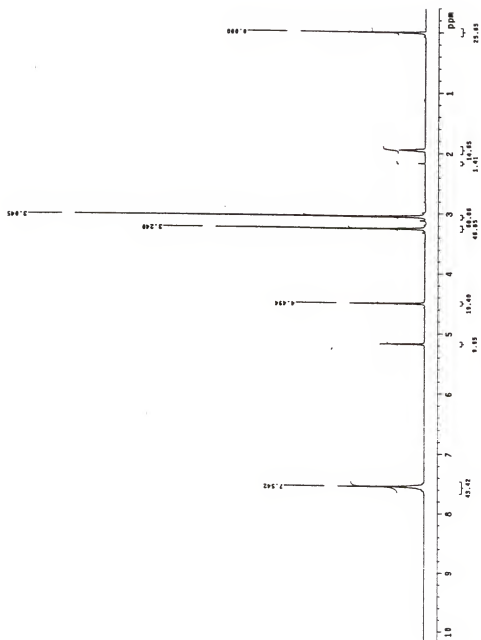


Figure A-6. De-methylation of 3-9 with 2eq. of I⁻ at 101°C, t = 0min

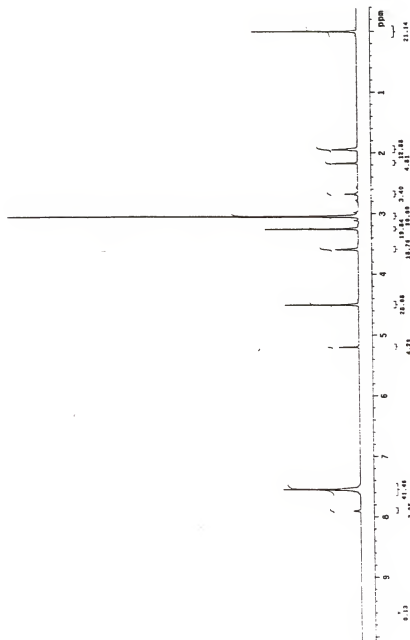


Figure A-7. De-methylation of 3-9 with 2eq. of I^- at 101°C , $t = 50\text{ min}$

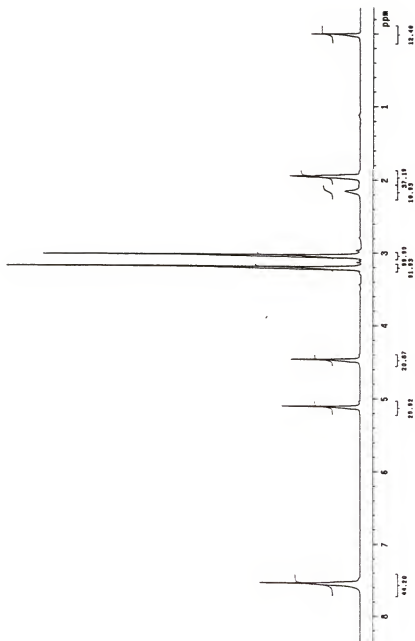


Figure A-8. De-methylation of 3-16 with 1eq. of I⁻ at 101°C, t = 0hr

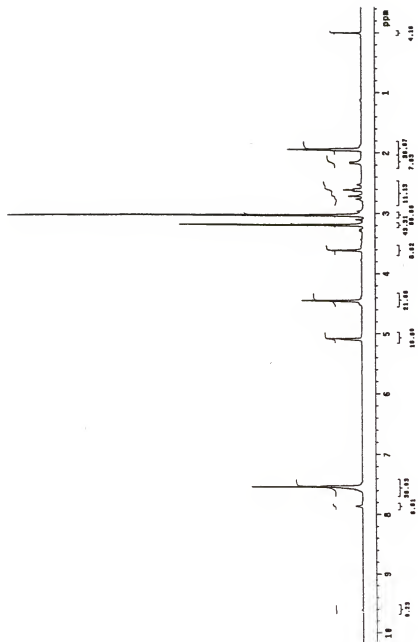


Figure A-9. De-methylation of **3-16** with 1eq. of I^- at 101°C , $t = 3\text{h}$

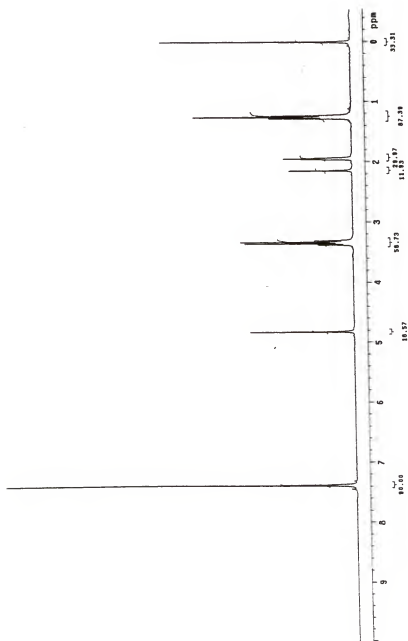


Figure A-10. De-ethylation of 3-15a with I^- at 101°C , $t = 0\text{h}$

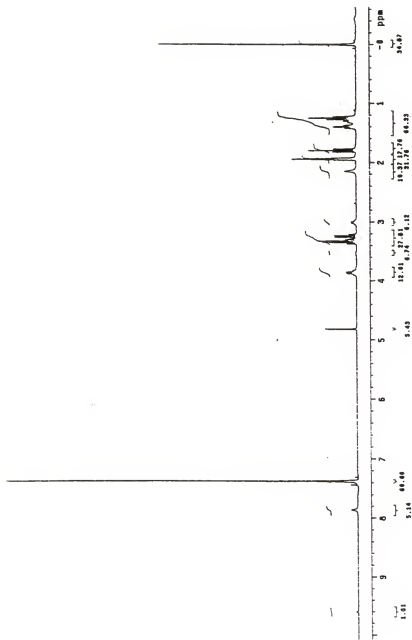


Figure A-11. De-ethylation of 3-15a with I⁻ at 101°C, t = 2h

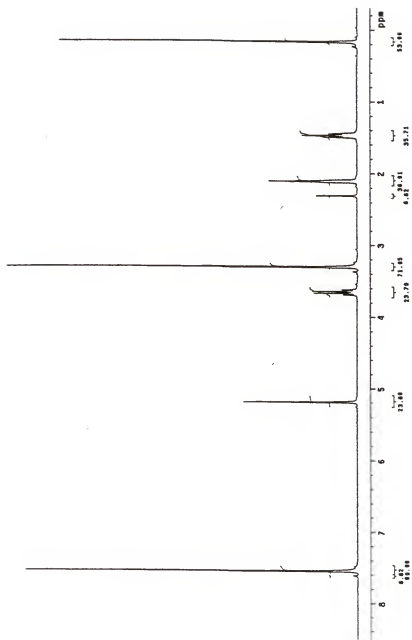


Figure A-12. De-alkylation of 3-15c with I^- at 101°C , $t = 0\text{h}$

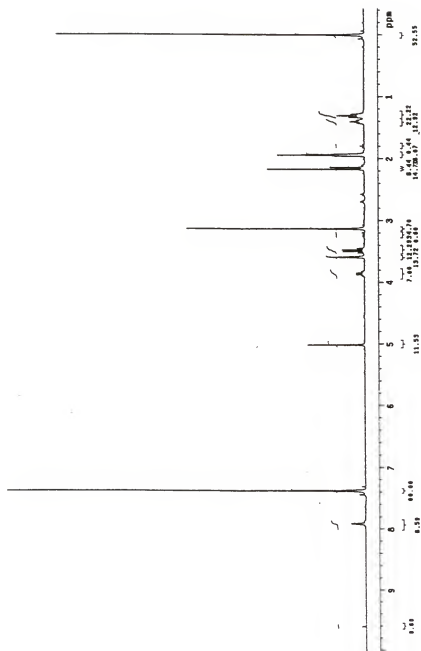


Figure A-13. De-alkylation of 3-15c with I^- at 101°C , $t = 3\text{h}$

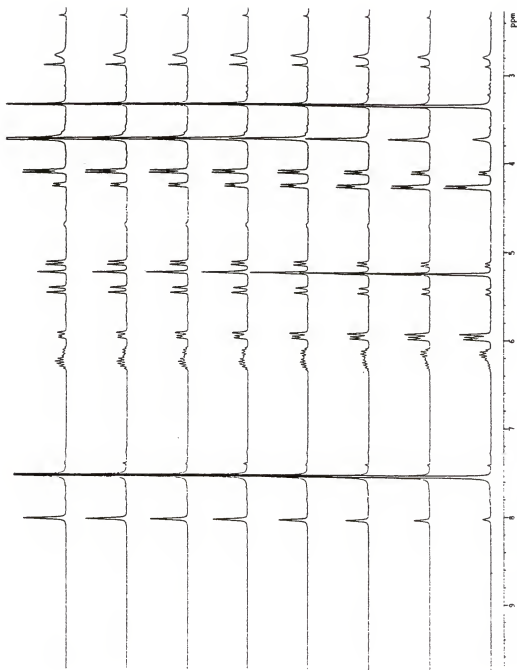


Figure A-14. De-allylation of 2-37 with 1eq. of I^- at 70°C at 10min intervals

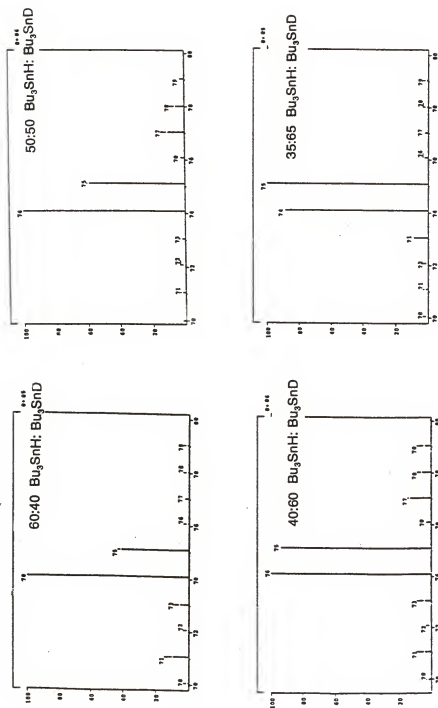


Figure A-15. Mass spectra from KIE study of 2-1

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BIOGRAPHICAL SKETCH

Michelle Fletcher was born March 9, 1969 in Jamaica, W.I. to Dennis and Hyacinth Fletcher. She has two older brothers and one younger sister. Michelle lived in Jamaica until she was seventeen years old, when she completed high school. She then moved to West Palm Beach, Florida where she attended Palm Beach Community College. From there, she went on to attend the University of Florida where she received a Bachelor of Arts degree in English and a Bachelor of Science degree in chemistry.

In 1992, while completing the requirements for her BS in chemistry, Michelle was selected to participate in the American Chemical Society's Summer R.E.U. program at the University of Florida. During that time, she was introduced to Professor William Dolbier, Jr. From that time on, she has performed research in numerous areas under Professor Dolbier's direction. Some of these areas include vinylcyclopropane rearrangements and reactivities of per-fluoroalkyl and distonic radicals.

Michelle is one of the founding members of the first NOBCCHE (National Organization for the Professional Advancement of Black Chemists and Chemical Engineers) chapter in Florida. The chapter was established at the University of Florida and is currently very active. She is also a member of the American Chemical Society.

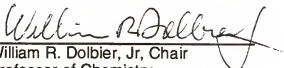
Michelle has given oral presentations at two national and two statewide chemistry conferences. In January of 1998, Michelle was awarded with the ACS Women's Travel Award to attend the 1998 215th National Meeting of the

American Chemical Society in Dallas, Texas. There, she gave an oral presentation entitled, "A Kinetic Study on the De-Alkylolation of Iodide on Ammonium Salts."

Not only has Michelle been active on the campus of the University of Florida, but she has also been very involved in her community. Whenever Michelle is not in her lab, she may be found working with children or singing in choirs. Michelle has served as choir director and Sunday School teacher for small children for three years. She has sung in two gospel choirs for ten years.

At the time of this writing, Michelle had accepted a position as Senior Research and Development Chemist with Albemarle Corporation in Baton Rouge, Louisiana.

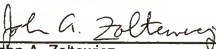
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William R. Dolbier, Jr, Chair
Professor of Chemistry

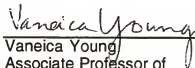
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Merle A. Battiste
Professor of Chemistry

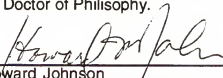
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John A. Zoltewicz
Professor of Chemistry

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Vaneica Young
Associate Professor of
Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.


Howard Johnson
Graduate Research Professor of
Microbiology and Cell Science

This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

August, 1998

Dean, Graduate School